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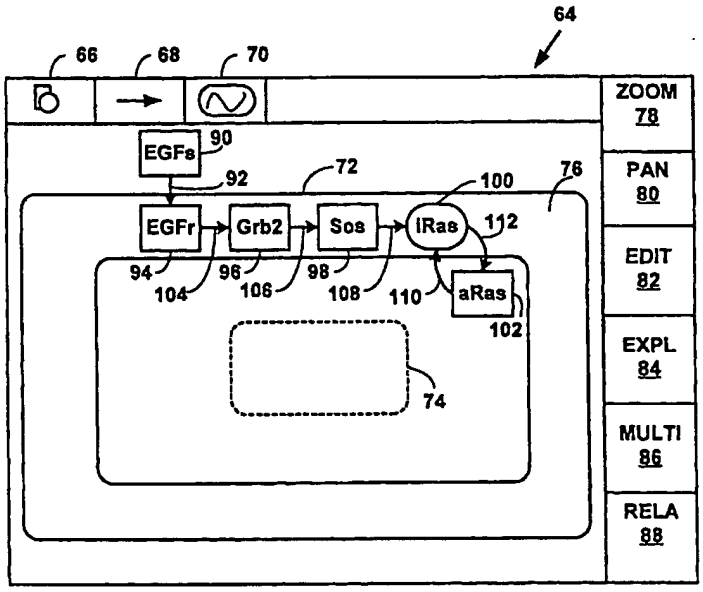
(54) Title: METHOD AND SYSTEM FOR DYNAMIC STORAGE RETRIEVAL AND ANALYSIS OF EXPERIMENTAL DATA WITH DETERMINED RELATIONSHIPS

(57) Abstract

A method and system for dynamic storage, retrieval and display of experimental information with determined relationships. A graphical user interface is presented from which shapes and arrows representing biological entities and transformations respectively, can be input and edited. Multidimensional information based on a pre-determined hierarchy is input to link the entities and transformations to additional information about the entities and transformations. Related information, if any, is input to link the entities and transformations to other information in plural external databases on a public network such as the Internet. Information associated with plural shapes connected with plural arrows is saved as a biological pathway with determined relationships in a database. The biological pathway defines a hierarchical representation of a biological function with determined relationships between entities and transformations. Biological pathway diagrams such as cell pathways with determined relationships may be dynamically input, edited and dynamically generated to represent biological functions, such as cellular functions, to enable a user to visually interact with identified dimensions of biological information. A user may dynamically navigate through identified dimensions of biological information to find out a relationship of a specific piece of biological information with other pieces of biological information. The method and system may help facilitate the abstraction of knowledge from information for biological pathways and provide new bioinformatic techniques.



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TITLE: METHOD AND SYSTEM FOR DYNAMIC STORAGE RETRIEVAL AND ANALYSIS OF EXPERIMENTAL DATA WITH DETERMINED RELATIONSHIPS

FIELD OF THE INVENTION

This invention relates to storing, retrieving and analyzing experimental information. More specifically, it relates to a method and system for dynamic storing, retrieving and analyzing experimental information with determined relationships.

BACKGROUND OF THE INVENTION

Traditionally, cell biology research has largely been a manual, labor intensive activity. With the advent of tools that can automate cell biology experimentation (see for example U.S. Patent Application SN 08/810,983 filed February 27, 1997, assigned to the same Assignee as the present application.) the rate at which complex information is generated about the functioning of cells has increased dramatically. As a result, cell biology is not only an academic discipline, but also the new frontier for large-scale drug discovery.

Cells are the basic units of life and integrate information from Deoxyribonucleic Acid ("DNA"), Ribonucleic Acid ("RNA"), proteins, metabolites, ions and other cellular components. New drug compounds that may look promising at a nucleotide level may be toxic at a cellular level. Thus, cell biology is becoming increasingly important to test now drug compounds. Florescence-based reagents can be applied to cells to determine ion concentrations, membrane potentials, enzyme activities, gene expression, as well as the presence of metabolites, proteins, lipids, carbohydrates, and other cellular components.

Innovations in automated screening systems for biological and other research are capable of generating enormous amounts of data. The massive volumes of feature-rich data being generated by these systems and the effective management and use of information from the data has created a number of very challenging problems. As is known in the art, "feature-rich" data includes data wherein one or more individual features of an object of interest (e.g., a cell) can be collected.

For more information on feature-rich cell screening see "High content fluorescence-based screening," by Kenneth A. Guiliano, et al., Journal of Biomolecular Screening, Vol. 2, No. 4, pp. 249-259, Winter 1997, ISSN 1087-0571, "PTH receptor internalization," Bruce R. Conway, et al., Journal of Biomolecular Screening, Vol. 4, No. 2, pp. 75-68, April 1999, ISSN 1087-0571, "Fluorescent-protein biosensors: new tools for drug discovery," Kenneth A. Giuliano and D. Lansing Taylor, Trends in Biotechnology, ("TIBTECH"), Vol. 16, No. 3, pp. 99-146, March 1998, ISSN 0167-7799.

To fully exploit the potential of data from high-volume data generating screening instrumentation, there is a need for new informatic and bioinformatic tools. As is known in the art, "bioinformatic" techniques are used to address problems related to the collection, processing, storage, retrieval and analysis of biological information including cellular information. Bioinformatics is defined as the systematic development and application of information technologies and data processing techniques for collecting, analyzing and displaying data obtained by experiments, modeling, database searching, and instrumentation to make observations about biological processes. How to present, organize and analyze the complex information about cell functioning so that new knowledge can be generated is critical for both pharmaceutical research and basic cell biology research.

There are several problems associated with using bioinformatic systems and techniques known in the art to capture and display biological information, such as cellular information. One problem is that biological information is typically collected and displayed as textual information in a uni-dimensional formation. This format prevents a user from visually

interacting with identified dimensions of biological information at the same time and dynamically navigating through those dimensions to find out the relationship of one piece of information with other pieces of information. This prevents the abstraction of knowledge from information.

Another problem is that biological pathways can not be adequately displayed with uni-dimensional textual information. Graphical representation of biological pathways is typically required to capture biological knowledge such as cellular knowledge. Biological pathway knowledge obtained from graphical representations is then typically used as a portal to unite other biological information, thus enabling the synthesis of new knowledge by investigating the inner relationship of this information.

Another problem is that bioinformatic systems known in the art only allow input and display of a small amount of uni-dimensional biological information. Such systems may use present only a subset of a total amount of known information associated with a biological entity or transformations. Another problem is that bioinformatic systems known in the art typically present a static graphical representation of a biological pathway cannot be input, edited or otherwise altered by a user. Another problem is that a user typically cannot navigate, expand or contract a portion of a presented biological pathway. Another problem is that collected biological information cannot be easily linked to other private or public databases to provide access to additional known or related information.

There have been attempts to solve some of these problems associated with inputting and displaying biological information associated with biological pathways. Such attempts include for example, "Ecocyc" from Pangea (see,

e.g., Nucleic Acids Research 26:50-53 (1998), Ismb 2:203-211 (1994)); "KEGG" pathway database from Institute for Chemical Research, Kyoto University (see, e.g., Nucleic Acids Research 27:377-379 (1999), Nucleic Acids Research 27:29-34 (1999)); "CSNDB" links to from Japanese National Institute of Health Sciences (see, e.g., Pac Symp. Biocomput 187-197 (1997)); "SPAD" from Graduate School of Genetic Resources Technology, Kyushu University, Japan; "PUMA" now called "WIT" from Computational Biology in the Mathematics and Computer Science Division at Argonne National Laboratory; and others. However, these solutions still suffer from one or more of the problems described above.

Thus, it is desirable to provide a bioinformatic system that enables the easy storage, retrieval and analysis of biological information associated with biological pathways. The bioiniformatic system should include the ability to dynamically input, edit and generate biological pathways and to provide the ability to access hierarchical information associated with the biological pathways from plural private and public databases.

SUMMARY OF THE INVENTION

In accordance with preferred embodiments of the present invention, some of the problems associated with inputting and displaying biological information associated with biological pathways are overcome. A method and system for dynamic storage, retrieval and display of experimental information with determined relationships is presented.

One aspect of the invention includes a method for storing experimental information with determined relationships. The method includes providing a graphical user interface from which shapes and arrows representing biological entities and transformations respectively, can be input and edited. Multi-dimensional information based on a pre-determined, but expandable hierarchy is input to link the entities and transformations to additional information about the entities and transformations. Related information, if any, is input to link the entities and transformations to other information in plural external databases on a public network such as the Internet. Information associated with plural shapes connected with plural arrows is saved as a biological pathway with determined relationships in a database. The biological pathway defines a hierarchical representation of a biological function with determined relationships between entities and transformations.

Another aspect of the invention includes a method for dynamically displaying experimental information with determined relationships. A biological pathway is selected from a list of biological pathways with determined relationships. A display mode is selected that is used to display

the biological pathway. A graphical representation including shapes and arrows representing entities and transformations respectively is dynamically generated using a first set of colors. The first set of colors is used to indicate a level of generalization in a hierarchy or a directed graph used to display the biological pathway with determined relationships.

Another aspect of the invention includes a system for dynamically storing, retrieving and displaying of experimental information with determined relationships. The system includes a graphical user interface and a database. The graphical user interface is used for dynamically inputting or editing information associated with biological pathway with determined relationships using shapes and arrows to represent entities and transformations and to capture information associated with biological pathway as it is drawn, for saving information associated with a biological pathway in a database, for retrieving information associated with selected biological entities or transformations from a database, for dynamically generating graphical representation of a biological pathway with multiple colors from information retrieved from a database, and for navigating through a hierarchy or a directed graph of information associated with a generated biological pathway.

The database is used for saving information associated with a plurality of shapes connected with a plurality of arrows as a biological pathway with determined relationships. The biological pathway defines a hierarchical representation of a biological function with determined relationships between the entities and transformations.

The present invention may provide the following advantages. Biological pathway diagrams with determined relationships may be

dynamically input, edited and dynamically generated to represent biological functions, such as cellular functions, to enable a user to visually interact with identified dimensions of biological information. A user may dynamically navigate through identified dimensions of biological information with different display colors to find out a relationship of a specific piece of biological information with other pieces of biological information. The biological pathways are linked to plural databases on local private and remote public networks (e.g. the Internet), including information related to the biological pathway. This may help facilitate the abstraction of knowledge from information.

The present invention may also be used to further facilitate a user's understanding of biological functions, such as cell functions, to design experiments more intelligently and to analyze experimental results more thoroughly. Specifically, the present invention may help drug discovery scientists select better targets for pharmaceutical intervention in the hope of curing diseases.

The foregoing and other features and advantages of preferred embodiments of the present invention will be more readily apparent from the following detailed description. The detailed description proceeds with references to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments of the present invention are described with reference to the following drawings, wherein:

FIG. 1 illustrates an exemplary experimental data storage system for storing experimental data with determined relationships;

FIGS. 2A and 2B are a flow diagram illustrating a method for storing experimental information with determined relationships;

FIG. 3 is a block diagram illustrating a screen display of a graphical user interface used to create, store and analyze biological pathways with determined relationships;

FIG. 4 is a block diagram illustrating an exemplary multi-dimensional hierarchy;

FIG. 5 is a block diagram illustrating an exemplary multi-dimensional hierarchy for a biological entity;

FIG. 6 is a block diagram illustrating an exemplary multi-dimensional hierarchy for a transformation;

FIG. 7 is a flow diagram illustrating a method for dynamically displaying experimental information including determined relationships;

FIG. 8 is a block diagram illustrating an exemplary multi-dimensional information page dynamically and created for a user in a summary display mode;

FIG. 9 is a block diagram illustrating an exemplary entity multi-dimensional information page dynamically created and displayed for a user in a dimension display mode;

FIG. 10 is a block diagram illustrating an exemplary related information page that dynamically created and displayed for a user in a link display mode; and

FIG. 11 is a flow diagram illustrating a method for dynamically displaying experimental information including determined relationships displaying from a remote computer.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Exemplary data storage system

FIG. 1 illustrates an exemplary experimental data storage system 10 for one embodiment of the present invention. The data storage system 10 includes one or more internal user computers 12, 14, (only two of which are illustrated) for inputting, retrieving and analyzing experimental data on a private local area network ("LAN") 16 (e.g., an intranet). The LAN 16 is connected to one or more internal proprietary databases 18, 20 (only two of which are illustrated) used to store private proprietary experimental information that is not available to the public.

The LAN 16 is connected to an internal database server 22 that is connected to one or more internal experimental information databases 24, 26 (only two of which are illustrated) comprising a private part and publicly part of a data store for experimental data. The internal database server 22 is connected to a public network 28 (e.g., the Internet). One or more external user computers, 30, 32, 34, 36 (only four of which are illustrated) are connected to the public network 28, to plural public domain databases 38, 40, 42 (only three of which are illustrated) and internal databases 24, 26 including experimental data and other related experimental information available to the public. However, more, fewer or other equivalent data store components can also be used and the present invention is not limited to the data storage system 10 components illustrated in FIG. 1.

In one specific exemplary embodiment of the present invention, data storage system 10 includes the following specific components. However, the present invention is not limited to these specific components and other similar

or equivalent components may also be used. The one or more internal user computers, 12, 14, and the one or more external user computers, 30, 32, 34, 36, are conventional personal computers that include a display application that provide a Graphical User Interface ("GUI") application (See FIG. 3). The GUI application is used to lead a scientist or lab technician through input, retrieval, analysis of experimental data with determined relationships and supports custom viewing capabilities. The GUI application also supports data exported into standard desktop tools such as spreadsheets, graphics packages, and word processors.

The internal user computers 12, 14, connect to the one or more private proprietary databases 18, 20, the database server 22 and the one or more or more internal databases 24, 26 over the LAN 16. In one embodiment of the present invention, the LAN 16 is a 100 Mega-bit ("Mbit") per second or faster Ethernet, LAN. However, other types of LANs could also be used (e.g., optical or coaxial cable networks). In addition, the present invention is not limited to these specific components and other similar components may also be used.

In one specific embodiment of the present invention, one or more protocols from the Internet Suite of protocols are used on the LAN 16 so LAN 16 comprises a private intranet. Such a private intranet can communicate with other public or private networks using protocols from the Internet Suite. As is known in the art, the Internet Suite of protocols includes such protocols as the Internet Protocol ("IP"), Transmission Control Protocol ("TCP"), User Datagram Protocol ("UDP"), Hypertext Transfer Protocol ("HTTP"),

Hypertext Markup Language ("HTML"), eXtensible Markup Language ("XML") and others.

The one or more private proprietary databases 18, 20, and the one or more internal databases 24, 26 are multi-user, multi-view databases that store experimental data. The databases 18, 20, 24, 26 use relational database tools and structures. The data stored within the one or more internal proprietary databases 18, 20 is not available to the public. Selected portions of the internal experimental information databases 24, 26, may be available to the public through database server 22 using selected security features (e.g., login, password, firewall, etc.

The one or more external user computers, 30, 32, 34, 36, are connected to the public network 28 and to plural public domain databases 38, 40, 42. The plural public domain databases 38, 40, 42 include experimental data and information in the public domain and are also multi-user, multi-view databases. The plural public domain databases 38, 40, 42, include such well known databases such as provided by Medline, Gen Bank, SwissProt, PDB, etc.

An operating environment for components of the data storage system 10 for preferred embodiments of the present invention include a processing system with one or more speed Central Processing Unit(s) ("CPU") and a memory. In accordance with the practices of persons skilled in the art of computer programming, the present invention is described below with reference to acts and symbolic representations of operations or instructions that are performed by the processing system, unless indicated otherwise. Such acts and operations or instructions are referred to as being "computer-executed" or "CPU executed."

It will be appreciated that acts and symbolically represented operations or instructions include the manipulation of electrical signals by the CPU. An electrical system represents data bits which cause a resulting transformation or reduction of the electrical signals, and the maintenance of data bits at memory locations in a memory system to thereby reconfigure or otherwise alter the CPU's operation, as well as other processing of signals. The memory locations where data bits are maintained are physical locations that have particular electrical, magnetic, optical, or organic properties corresponding to the data bits.

The data bits may also be maintained on a computer readable medium including magnetic disks, optical disks, organic memory, and any other volatile (e.g., Random Access Memory ("RAM")) or non-volatile (e.g., Read-Only Memory ("ROM")) mass storage system readable by the CPU. The computer readable medium includes cooperating or interconnected computer readable medium, which exist exclusively on the processing system or be distributed among multiple interconnected processing systems that may be local or remote to the processing system.

Storing experimental information with determined relationships

FIGS. 2A and 2B are a flow diagram illustrating a Method 46 for storing experimental information with determined relationships. In FIG. 2A at Step 48, a shape is selected from a menu on graphical user interface on a computer. The shape represents an entity that participates in a biological pathway. At Step 50, the shape is placed at a desired location in an electronic window on the graphical user interface. At Step 52, an arrow is selected from the graphical user interface. The arrow represents a transformation between

entities that participate in a biological pathway. At Step 54, the arrow and the shape are connected. This provides a graphical representation of a transformation of an entity with a determined relationship. At Step 56, multi-dimensional information is input to link the shape and arrow to multi-dimensional information specifying entity and transformation. The multi-dimensional information is stored in a database with a pre-determined format.

In FIG. 2B at Step 58, related information, if any, is input to link the shape and arrow to other information related to the entity and transformation from plural external databases. At Step 60, a test is conducted to determine if a desired number of iterations of Steps 50, 52, 54, 56 and 58 have been completed. If so, at Step 62, information associated with the plural shapes connected with plural arrows is saved in a database as a biological pathway with determined relationships between entities and transformations. If a desired number of iterations have not been completed at Step 60, a loop continues at Step 48 of FIG. 2A until the desired number of iterations has been completed. The biological pathway defines a hierarchical representation of a biological function with determined relationships between entities and transformations.

In another embodiment of the present invention, Method 46 allows all shapes for all entities selected and placed at one time. In such an embodiment, a loop would be entered to repeat steps 48 and 50 a desired number of times, and then Step 62 would be executed. (not illustrated in FIG. 2).

In another embodiment of the present invention, Method 46 allows arrows for all transformations to be connected to entities at one time. In such an embodiment, a loop would be entered to repeat steps 52 and 54 a desired

number of times, and then Step 62 would be executed (not illustrated in FIG. 2).

Either of these embodiments, all shapes and/or all arrows would be input at one before any multi-dimensional information, or any related information is input. This allows a user to spatially layout one or more desired biological and then go back and input the multi-dimensional and/or related information at a later time.

In one embodiment of the present invention only an indication of the types of shapes and arrows and their absolute or relative locations on the graphical user interface is saved in the database. In such an embodiment, when the saved biological pathway is displayed, the shapes are arrows representing entities and transformations with determined relationships are dynamically re-generated from the saved information. Such an embodiment requires less storage space to store biological pathway and also allows for a quicker re-generation and display of a saved biological pathway with determined relationship. In another embodiment of the present invention, the graphical shapes and arrows are saved in the database along with the associated information.

FIG. 3 is a block diagram illustrating a screen display of a Graphical User Interface ("GUI") 64 used to create, display and analyze biological pathways with Method 64 (FIGS. 2A and 2B). The GUI 64 includes a graphical button for selecting a shape 66, selecting an arrow 68, and selecting a cell organelle or compartment 70. The GUI 64 also illustrates an outline of a cell 72, an outline of a nucleus 74 within the cell 72, and an outline of a cell membrane 76. The cell membrane 76 is exaggerated in FIG. 3 to present a

specific example of a cell signaling pathway in the cell membrane 76. FIG. 3 illustrates only one cell 72. However, the present invention is not limited to one cell and multiple cells, multiple organelles and multiple compartments, inside and outside of a cell can also be illustrated with GUI 64.

GUI 64 further comprises a graphical button for zooming in and out 78, panning 80, editing a new or a previously saved biological pathway 82, exploring a saved biological pathway 84, specifying and/or examining multi-dimensional information associated with a pathway 86 and its components, and examining related information associated with a biological pathway 88 and its componets. However, the present invention is not limited to a GUI 64 with the graphical buttons and associated functionality illustrated in FIG. 3 and more, fewer or equivalent graphical buttons and functionality can also be used.

In one embodiment of the present invention, shape graphical button 66 on the GUI 64 provides a menu for shapes including rectangles, ovals, circles, hexagons, pie-shapes or other shapes to be selected. The different shapes represent different types of biological entities. For example, the rectangles represent active entities. The ovals represent inactive entities. The circles represent entity inhibitors. The hexagons represent factors exchanged between entities. The pie-shapes represent intermediate entity transformation products. However, the present invention is not limited to the shapes or entities listed, and more fewer or equivalent entities can also be represented by more fewer or equivalent shapes.

The arrows represent biological transformations. The biological transformations include, for example, transcription factor activation, cellular

hypertrophy, protein kinase activation, protease activation, gene expression, receptor activation, apoptosis, material translocation such as internalization of cell surface receptor proteins, mitochondrial potential, neurite outgrowth, cell viability or a miotic index for a cell. However, the present invention is not limited to this list of biological transformations and more, fewer or equivalent biological transformations can also be represented by the arrows.

The cell organelle and compartment graphical button 70 allows graphical representations of cell organelles and compartments including, chromosomes, nucleolus, mitochondria, golgi bodies, ribosomes, micro-tubules, smooth endoplasmic reticulum, rough endoplasmic reticulum, and other cell organelles to be created. Compartments, such a region surrounding a stress fiber, can be defined as needed by specific biological pathways. However, more, fewer or equivalent cell organelles and compartments can also be used and the present invention is not limited to the cell organelles listed. The cell organelles and compartments may participate in selected biological pathways or be the location of compartments of selected pathways.

Method 64 (FIG. 2) is illustrated with GUI 64 (FIG. 3) with a portion of a extracellular Epidermal Growth Factor ("EGF") signaling pathway known in the biological arts. However, the present invention is not limited to this specific example associated with this specific signaling pathway and virtually any biological pathway can be used with Method 46 and GUI 64. As is known in the biological arts, a biological pathway is a pathway for any biological entity and any transformation upon or between biological entities.

In such a specific embodiment in FIG. 2A at Step 48, the edit graphical button 82 is selected from GUI 64 to input a new biological pathway. A shape

90 is selected using the shape graphical button 66 on GUI 64 (FIG. 3), wherein the shape 90 represents an entity that participates in the EGF cell signaling pathway. At Step 50, the shape 90 is placed at a desired location in an electronic window on the GUI. For example, a rectangle 90 (FIG. 3) is selected using shape graphical button 66 menu and placed outside the cell outline 72. In this specific example, the rectangle 90 represents an active extracellular EGF signaling molecule ("EGFs") that initially effects the cell 72 from outside the cell 72.

At Step 52, an arrow 92 is selected from the arrow graphical button 68 on the GUI 64. The arrow 92 represents a transformation between entities that participate in a pathway. At Step 54, the arrow and the shape are connected. This provides a graphical representation of a transformation of an entity with a determined relationship to the cell 72 (i.e., extracellular signal) as is illustrated in FIG. 3.

At Step 56, multi-dimensional information is input to link the shape and arrow to multi-dimensional information specifying the entity and transformation. In one embodiment of the present invention, general multi-dimensional information is input at Step 56 and is organized in a hierarchical fashion that allows electronic links to other associated information. In one embodiment of the present invention, the general multi-dimensional information includes, general information for a species, an experimental system, functional types to classify an entity, transformation types to classify a transformation, and a compartment where an entity or transformation occurs (See FIG. 4). However, more, fewer or equivalent dimensions and other multi-dimensional information can also be input.

In one embodiment of the present invention, when a user is creating a biological pathway and selects a shape or arrow, (e.g., by "clicking" on it), an electronic input form is presented to the user so the user can input any known general multi-dimensional information about an entity or transformation.

In such an embodiment, an electronic input form created in the Hyper Text Mark-up Language ("HTML"), or the eXtensible Mark-up Language ("XML") or other hardware independent mark-up languages known in the art is displayed for a user. However, virtually any programming language can be used to create and display the electronic input form (e.g., C, C++, Visual Basic, Visual C++, Java, etc.) and the present invention is not limited to hardware independent mark-up languages. The user then inputs any known general multi-dimensional information for the entity or transformation.

FIG. 4 is a block diagram illustrating an exemplary general multi-dimensional hierarchy 114 for used to input multi-dimensional information at Step 56. However, the present invention is not limited to this exemplary general hierarchy, and other types or equivalent multi-dimensional information storage schemes can also be used to input multi-dimensional information at Step 56.

In addition, the general multi-dimensional information can be represented with a directed graph. As is known in the computer science arts, a "directed graph" is a graph whose edges have a direction. An edge in a directed graph not only relates two nodes in a graph, but it also specifies a predecessor-successor relationship. A "directed path" through a directed graph is a sequence of nodes, $n_1, n_2, \ldots n_k$, such that there is a directed edge from n_i to n_{i+1} for all appropriate i. The general multi-dimensional information

can be represented exclusively by a hierarchy, exclusively by a directed graph, by both a hierarchy and a directed graph, or any combination thereof.

The hierarchy 114 includes, a species 116 (e.g., human), an experimental system 118 (e.g., skeletal system), functional types 120 including classifications for biological entities (e.g., organ, tissue, cell, sub-cell component, molecule) and transformation types 122 including classifications of transformations and a level for a compartment 124 where an entity or transformation occurs. This multi-dimensional information is stored in an internal database (e.g., 18,20,24,26). Each component in the hierarchy 114 represents a hierarchy, so hierarchy 114 actually includes five parallel hierarchies.

FIG. 5 is a block diagram illustrating an exemplary multi-dimensional hierarchy 126 for a functional type including a biological entity (e.g., a cell) from hierarchy 114. In addition, the multi-dimensional information for a biological entity can also be represented with a directed graph or a combination of a hierarchy and/or a directed graph as was described above. However, the present invention is not limited to this exemplary hierarchy, and other types or equivalent multi-dimensional information storage schemes can also be used to input multi-dimensional information for an entity.

In one embodiment of the present invention, a separate hierarchy for providing specific multi-dimensional information a biological entity or a transformation is not used. Only the general hierarchy 114 is used. In another embodiment of the present invention, separate specific hierarchies are used for both biological entities and transformations to specific further provide multi-dimensional information about an entity or a transformation.

The entity hierarchy 126 includes a first level for a biological entity 128. A second level includes a component view 130, a morphology 132 of the biological entity 128, an optional electron microscope ("EM") photograph 134 and an optional fluorescent view 136 of the biological entity 128. The component view 130 includes a third level. The third level includes basic information 138, site information 140, function information 142, enzyme information, if any, 144, reaction information 146, transport system information 148 and a pathway view 150. Multi-dimensional information that is input for a biological entity 128 is stored in a local database using the hierarchy 126.

In one embodiment of the present invention, the biological entity 128 is assumed to be a sub-component of a cell, or a cell. In another embodiment of the present invention, the hierarchy 126 also includes additional levels above the first level for the biological entity 128 from lowest to highest for tissues, organs, systems, or organisms. These additional levels are not illustrated in FIG. 4, but may also be used to input and display specific multi-dimensional information for an entity.

In such an embodiment, an aggregation of plural cells comprise a tissue. An aggregation of plural tissues comprise an organ. An aggregation of plural organs comprise a system. An aggregation of plural systems comprise an organism. An aggregation of plural organism comprise a species.

In one embodiment of the present invention, when a user is creating a general biological pathway and selects a shape, (e.g., by "clicking" on it), an input electronic form for hierarchy 114 and/or a transformation hierarchy is

presented to a user, so the user can input any known multi-dimensional information.

In such an embodiment, an electronic input form is created in the HTML or XML or other hardware independent mark-up languages known in the art is displayed for a user. However, virtually any programming language can be used to create and display the electronic input form (e.g., C, C++, Visual Basic, Visual C++, Java, etc.) and the present invention is not limited to hardware independent mark-up languages. The user then inputs any known general multi-dimensional information for the entity or transformation. The user then inputs any known general or specific multi-dimensional information for an entity or transformation.

Not all of the categories of multi-dimensional information can be input for every biological entity 128. For some biological entities 128, all of the categories of multi-dimensional information may be known. For other biological entities 128, only some of the categories multi-dimensional information may be known, so only the known information is input.

Table 1 illustrates exemplary general multi-dimensional information input that maybe by a user at Step 56 for general multi-dimensional hierarchy 114 for the exemplary EGF pathway. However, the present invention is not limited to the general multi-dimensional information illustrated in Table 1 or the hierarchy 114 for inputting general multi-dimension information. More, less or equivalent general multi-dimensional information can be used.

Category	Description
Species 116	Human
Experimental System 118	Skeletal Muscle
Functional Type of Entity 120	EGF, EGF receptor
Transformation 122	EGF binding to EGF receptor
Compartment 124	Cell membrane

Table 1.

Table 2 illustrates exemplary specific multi-dimensional information that may be input by a user for EGF signaling molecule 90 (i.e., a functional type for an entity) at Step 56 based on the entity hierarchy 126 (FIG. 5). However, the present invention is not limited to the multi-dimensional information illustrated in Table 2 or the entity hierarchy 126.

In addition, a morphology 132 of the biological entity 128, an optional electron microscope ("EM") photograph 134 and an optional fluorescent view 136 of the biological entity 128 may also be input by a user (e.g., by inputting a link to a file or location including such information).

Category	Description
Basic Information 138	EGF 78 is a globular protein of 6.4 kDa comprising 53 amino acids. It includes three intra-molecular disulfide bonds essential for biological activity.
Site 140	Extracellular signaling molecule.
Function 142	Activates encoding of an intrinsic tryosine-specific protein kinase activity. This kinase activity catalyses the transfer of the gamma-phosphate of ATP to a tryosine resiude of the receptor and also of some other intra-cellular proteins.
Enzyme 144	Tryosine-specific protein kinase
Reactions 146	The EGF precursor is N-glycosylated and contains a hydrophobic domain allowing it to be anchored in the cell membrane. In cells that do not cleave this precursor (e.g., Kidney cells), the membrane-bound form of the precursor may itself serve as a receptor for yet unknown ligands. EGF 78 may be involved in Juxtacrine growth control mechanisms.
Transport System 148	NA
Pathways 150	NA

Table 2.

FIG. 6 is a block diagram illustrating an exemplary multi-dimensional hierarchy for a transformation 152. The transformation hierarchy 152 includes a first level for a transformation identifier 154, type 156, name 158, role 160,

and group type 162. The transformation hierarchy includes a second level for a transformation input 164, output 166, key 168, and effectors 170. Multi-dimensional information input for a transformation is stored as a local database. In addition, the multi-dimensional information for a transformation can also be represented with a directed graph or a combination of a hierarchy and/or a directed graph as was described above. However the present invention is not limited to this exemplary transformation hierarchy and have fewer or equivalent transformation levels can also be used.

Table 3 illustrates exemplary specific multi-dimensional information input by a user for the transformation 92 from EGF signaling molecule 90 at Step 56 based on the transformation hierarchy 152 (FIG. 6). However, the present invention is not limited to the specific multi-dimensional information illustrated in Table 3 or the transformation hierarchy 152.

Category	Description
Transformation Identifier 156	EGFs
Type 158	Receptor/ligand interaction
Name 160	EGF
Role 162	Extracellular signaling
Group Type 164	Currently used for a group of transformations. A group type can be simultaneous, coupled, etc.
Input 166	EGF molecule 90, EGF receptor
Output 168	EGF, EGR receptor complex
Key 170	EGF1
Effectors 172	EGF receptor 94

Table 3.

In one specific embodiment of the present invention, when the shape or arrow is placed at a location on the GUI 64, it is placed with a first color (e.g., red). When multi-dimensional information is input, the shape or arrow is changed from a first color to second color (e.g., green). The colors allow a user to visually determine if multi-dimension information has been input for the entity or transformation. The second color allows a user to visually

determine an aggregated view of the multi-dimensional information for the shape or arrow.

In FIG. 2B at Step 58, related information, if any, is input to link the shape and arrow to other information related to the entity and transformation from plural external databases. In one exemplary embodiment of the present invention, the related information is input and stored in a hierarchy. In another exemplary embodiment of the present invention, the related information is input and stored in a non-hierarchical manner.

In one exemplary embodiment of the present includes specifying related information including information about entities, including detailed information such as assays including an experimental protocol used to test the entity or transformation; compounds, including compounds that are effective on selected entities or transformations; diseases, including known diseases that are related to the selected entities or transformations; authors, including other authors who have expertise in the selected entities or transformations; expression, including gene expression related to the selected entity or transformation; validation, including a level of credibility of the existence and role of the selected entity or transformation; or other pathways, including other pathways that the selected entities or transformations participate in. However, more or fewer related information can also be specified and the present is not limited to this list of related information.

In one embodiment of the present invention, a validation level is assigned in one of two ways: (1) manual assignment by an editorial board; or (2) using an automated method. If manual assignment is completed, an editorial board made up of scientists will confer to manually assess the

credibility of the information associated with an entity or transformation. A validation weight (e.g., from zero to ten) is assigned. A validation weight of zero indicates a lowest level of validity for the information (e.g., results from a single experiment). A validation weight of ten indicates a very high level of validity for the information (e.g., similar results obtained from many different experiments).

If automatic assignment is completed, an automated method is used to take into account multiple pre-determined factors that contribute to the validity of a piece of biological information. The predetermined factors are evaluated to calculate a validation weight. The pre-determined factors may include, but are not limited to, such factors as a number of experiments or references used to create the information, a quality of a source of an experiment or reference, what type of experiment was used to acquire the information, a reputation, if any, of the researcher that supplied the information, etc.

In one embodiment of the present invention, when a user is creating a biological pathway and has selected a shape or arrow, (e.g., by "clicking" on it), an input form is presented to the user so the user can input any known related information for an entity or transformation.

In such an embodiment, an electronic input form created in HTML, XML or other hardware independent mark-up languages known in the art is displayed for a user. However, virtually any programming language can be used to create and display the electronic input form (e.g., C, C++, Visual Basic, Visual C++, Java, etc.) and the present invention is not limited to hardware independent mark-up languages. The user then inputs any known related information.

As was discussed above for multi-dimensional information, not all categories of related information can be input for every entity. For some entity all of the categories of related information may be known. For other entities, only some of related information may be known, so only known information is input. For still other entities, none of the categories of related information may be known, so no related information will be input.

Table 4 illustrates exemplary related information input by a user for EGF signaling molecule 90 at Step 58. However, the present invention limited to the related information illustrated in Table 4.

Category	Description
Assays 220	NA
Compounds 222	NA
Diseases 224	Human Cancers
Authors 226	Shigeo Tsuchiya, et al., Solution Structure of SH2 Domain of Grb2/Ash Complexed with EGF Receptor-Derived Phosphotyrosine-Containing Peptide, J. Biochem. 125, 1151-1159 (1999).
Expression 228	NA
Validation 230	10
Other Pathways 232	PDGF

Table 4.

In one specific embodiment of the present invention, when related information is input, if any, the shape is changed from a second color (e.g., green) to a third color (e.g., blue). The third color allows a user to visually determine if both multi-dimensional and related information has been input for the shape.

Returning to FIG. 2B at Step 60, a test is conducted to determine if a desired number of iterations of Steps 50, 52, 54, 56 and 58 have been completed. If a desired number of iterations have not been reached at Step 60, a loop continues at Step 48 of FIG. 2A until the desired number of iterations has been completed.

In this specific example Steps 50, 52, 54, 56 and 58 are repeated five times adding shapes 94, 96, 98, 100 and 102 with connecting arrows 104, 106, 108, 110 and 112, respectively, via the GUI 64 of FIG. 3. In this specific illustrative example, shape 94 represents an active entity for an EGF receptor ("EGFr"). Shape 96 represents an active entity for a Growth factor receptor bound protein 2 ("Grb2"). Shape 98 represents an active entity for Son of sevenless ("Sos"). Shape 100 represents an inactive entity for Ras ("iRAS"). Shape 102 represents an active entity for Ras ("aRAS"). The function of these shapes as used in the exemplary EGF pathway is explained below.

As is known in the biological arts, the EGF receptor 94 is a 170 kDa transmembrane glycoprotein. An extra cellular receptor domain contains an EGF binding site and also binds mammalian TGF-alpha. An intracellular receptor domain encodes an intrinsic tyrosine-specific protein kinase. This kinase catalyses the transfer of the gamma-phosphate of ATP to a tyrosine residue of the receptor and also of some other intracellular proteins. The intracellular kinase domain of the EGF receptor 94 is activated by binding of EGF or TGF-alpha to the extracellular receptor domain. The EGF receptor 94 is also phosphorylated by protein kinase-C at serine and threonine residues.

Grb2 96 is an adaptor protein with a domain structure (SH3-SH2-SH3). The two SH3 domains bind to protein sequences in a carboxyl terminal region of a guanine nucleotide to exchange Sos 98. Upon EGF stimulation 90, Grb2 96 binds to the EGR receptor 92 directly or indirectly through proteins such as Shc, FAK, Syp and IRS-1, by recognizing phosphotyrosine-containing sequences to allow interaction with inactive Ras 100.

Sos 98 is a guanine nucleotide exchange factor for inactive Ras 100 that binds to Grb2 96. Sos 98 mediates the coupling of receptor tyrosine kinases for inactive Ras 100 activation. Sos 98 is also associated with ligand-activated tyrosine kinase receptors which bind Grb2 96. At the cell membrane 76, Sos 98 can catalyze the exchange of GDP for GTP bound to inactive Ras 100, thereby activating active Ras 102 from inactive Ras 100.

Ras 100,102 is a super-family of small GTPases including a single GTPase domain. Ras is active 102 in its GTP bound state. Ras is inactive 100 in its GDP state. Ras 100,102 activity is positively regulated by EGF's 90. Inactive Ras 100 proteins are generally associated with cell membranes 76 via prenylation near their C-terminus. Active Ras 102 proteins are generally associated with cell cytoplasm.

A desired number of iterations have been completed at Step 60 when a portion of a biological pathway or a complete biological pathway has been input. In the specific example, after five iterations at Step 62, information associated with the plural shapes connected with plural arrows is saved as a biological pathway with pre-determined relationships in database in a pre-determined format.

In one exemplary preferred embodiment of the present invention, information associated with a biological pathway, whose structure is defined by a hardware independent XML Document Type Definition ("DTD") that is stored in a local file. A specific exemplary XML document used to store a biological pathway is illustrated in Table 5. However, the present invention is not limited to the XML DTD in Table 5 or to storing a biological pathway in an XML format and other similar or equivalent formats can also be used.

```
<!--A DTD for cellular pathway information: PML.dtd
<!--Author(s):        Jian Wang -->
<!-- Copyright © 1999, Cellomics, Inc. All rights reserved.-->

<!ELEMENT Pathways (Pathway*)>

<!-- ref defines the references used in an xml doc. Reflink at this level
links to the references that is generic to the whole pathway. Reflink at other levels are
references specific to that level -->

<!ELEMENT Pathway
((BioSysIComponent|Cell_Compartment|Cellular-Process|Functional-unit|Transformat
ionsIFeatureinfolRef)*,RefLink?, Notes*)>
<!ATTLIST Pathway
Pathway-ID ID #REQUIRED
PathwayName CDATA #IMPLIED>

<!ELEMENT BioSys (Organism?,System?,Organ?,Tissue?,Cell?,Notes*)>

<!ATTLIST BioSys
BioSys - ID ID #REQUIRED>
<!ELEMENT Organism EMPTY>
<!ATTLIST Organism
Organism CDATA #REQUIRED
DevStage CDATA #IMPLIED>
<!ELEMENT System EMPTY>
<!ATTLIST System
System CDATA #REQUIRED
DevStage CDATA #IMPLIED>
<!ELEMENT Organ EMPTY>
<!ATTLIST Organ
Organ CDATA #REQUIRED
DevStage CDATA #IMPLIED>
<!ELEMENT Tissue EMPTY>
<!ATTLIST Tissue
Tissue CDATA #REQUIRED
DevStage CDATA #IMPLIED>
<!ELEMENT Cell EMPTY>
<!ATTLIST Cell
Cell CDATA #REQUIRED
CellCycleStage CDATA #IMPLIED
DevStage CDATA #IMPLIED>


<!ELEMENT Cell - Compartment (#PCDATAINotes)*>
<!ATTLIST Cell Compartment
Compartment - ID ID #REQUIRED
Compartment-Name CDATA #REQUIRED>


<!ELEMENT Cellular Process (#PCDATAINotes)*>
<!ATTLIST Cellular Process
Process ID ID #REQUIRED
Process-Name CDATA #REQUIRED>

<!ELEMENT Component ((Abbreviation|Modification|Synonym)*, Notes*)>
```

```
<!ATTLIST Component

Component ID ID #REQUIRED

Component Name CDATA #REQUIRED BioSys IDREF #REQUIRED>

<!ELEMENT Modification (#PCDATA|Notes)*>

<!ATTLIST Modification

Modification Site CDATA #IMPLIED Modification_Type CDATA #REQUIRED>

EMENT Functional - Unit (ComponentLink*, Synonym*, RefLink?, Notes*)> <!ATTLIST Entity
Functional Unit
Unit ID ID #REQUIRED
Unit Name CDATA #REQUIRED
Unit-Abbr CDATA #IMPLIED
BioSys IDREF #REQUIRED
X Coord CDATA
Y-Coord CDATA #IMPLIED
Shape (CIRCLE|POLYGON|SQUARE|OVAL|RECTANGLE) "CIRCLEII>

<!-- the following "SimpleLink" points to the ID of a defined component or functional - unit
or cell_compartment or cellular_process. The above can be accomplished by using
IDREF instead of Simple Links. However, it may be more extensible using links since we
know that the component definitions will be on the server somewhere (outside of any
specific xml doc) in the future. -->
LEMENT ComponentLink (SimpleLink, Notes*)> <!ATTLIST ComponentLink
NumberOfComponent CDATA #IMPLIED
InCompartment IDREF #REQUIRED
UniformInCompartment (TRUE|FALSE) "TRUE">

<!ELEMENT Synonym (Abbreviat-i-on*, Notes*)>
<!ATTLIST Synonym
Synonym DDATA #REQUIRED>
<!ELEMENT Abbreviation (#PCDATA|Notes)*>
<!ATTLIST Abbreviation

Abbreviation CDATA #REQUIRED>

<!-- having a RefLink element is for the sole purpose of making the xml doc more
readable; otherwise one would not know what the extended link is all about since the
"ExtendedLink" element is reused extensively. In this case, the href attribute should point
to some defined reference in the same xml doc using XPointers: "#IDo"-->
<!ELEMENT RefLink (ExtendedLink)>

LEMENT Ref ((Publication|Person|Organization)*, Notes*)> <!ATTLIST Ref
Ref ID ID #REQUIRED
Date-Month CDATA #IMPLIED
Date-Day CDATA #IMPLIED
Date-Year CDATA #IMPLIED>

<!-- the following simplelink links to a medline record --> <!ELEMENT Publication
(Person*, SimpleLink, Note?)>

<!ATTLIST Publication

Title CDATA #IMPLIED

Journal CDATA #IMPLIED
```

```
Publisher CDATA #IMPLIED
PageStart CDATA #IMPLIED
PageEnd CDATA #IMPLIED
Volume CDATA #IMPLIED
Issue CDATA #IMPLIED
Type CDATA #IMPLIED
Date - month CDATA #IMPLIED
Date_Day CDATA #IMPLIED
Date - Year CDATA #IMPLIED >

<!ELEMENT Person (Organization*, Notes*)> <!ATTLIST Person .
FirstName CDATA #IMPLIED

MiddleInit CDATA #IMPLIED
LastName CDATA #IMPLIED

StreetAddress CDATA #IMPLIED
City CDATA #IMPLIED

State CDATA #IMPLIED

ZipCode CDATA #IMPLIED
AreaCode CDATA #IMPLIED
PhoneNum CDATA #IMPLIED
Ext CDATA #IMPLIED
Email CDATA #IMPLIED
Web CDATA #IMPLIED

Role CDATA #IMPLIED>

<!ELEMENT Organization (#PCDATAINotes)*>

<!ATTLIST Organization

Name CDATA #REQUIRED
Type (commerciallAcademiciGovernment) #REQUIRED>



<!-- "Role" describes the function of some item in a collection, such as "rate limiting,, -->


<!ELEMENT Transformations ((TransformationITransformationsIEffectors)*,
RefLink?, Notes*)>

<!ATTLIST Transformations

Transformations - ID ID #REQUIRED

Transformations-Type CDATA #IMPLIED
Transformations Name CDATA #IMPLIED
Role CDATA #IMPLIED

        Group_Type CDATA #IMPLIED>


<!ELEMENT Transformation (Input+,Output+,Effectors*,RefLink?, Notes*)>
<!ATTLIST Transformation
```

```
Transformation ID ID #REQUIRED

TransformationType CDATA #IMPLIED
Transformation Name CDATA #IMPLIED
Role CDATA #IMPLIED>

<!-- Input, Output and Effector reference Unit -->
<!ELEMENT Input (#PCDATAINotes)*>
<!ATTLIST Input
Input_ID IDREP #REQUIRED>
<!ELEMENT Output (#PCDATAINotes)*>


<!ATTLIST Output

        Output - ID IDREF #REQUIRED>
        <!ELEMENT Effectors (Effector+, Notes*)>
        <!ATTLIST Effectors
        Group Type (synergismlxyz) "synergism,,>
        <!ELEMENT Effector (#PCDATAINotes)*>
<!ATTLIST Effector
Effector ID IDREF #REQUIRED
Effect-Type CDATA #IMPLIED
Role CDATA #IMPLIED
Is-Positive (TRUEIFALSE) "TRUE">



<!-- Feature-ID references an object of the type specified by Feature_Type -->
<!ELEMENT FeatureInfo (ExtendedLink, Notes*)>
        <!ATTLIST FeatureInfo
                Feature ID              IDREF #REQUIRED
                Feature Type            (ComponentlunitiTransformations)
                Info_Type

(EntitylAssaylCompoundIReferencelPathwaylDiseaselCredibility) "Entity">

<!ELEMENT ExtendedLink (LinkLocator*, Notes*)>
<!ATTLIST ExtendedLink
XML-LINK CDATA #FIXED "EXTENDED"
                ROLE CDATA #IMPLIED
                TITLE CDATA #IMPLIED
                INLINE (TRUEIFASLE)             "TRUE"
                SHOW (EMBEDIREPLACEINEW)                "REPLACE"
                ACTUATE (AUTOJUSER)             "USER">

<!ELEMENT LinkLocator (#PCDATAINotes)*>

<!ATTLIST LinkLocator -

XML-LINK CDATA #FIXED "LOCATOR-'
ROLE CDATA #IMPLIED

HREF CDATA #REQUIRED

TITLE CDATA #IMPLIED

SHOW (EMBEDIREPLACEINEW)    "REPLACE"
```

```
ACTUATE (AUTOJUSER)    "USER">

<!ELEMENT SimpleLink (#PCDATAINotes)*>

<!ATTLIST SimpleLink

XML-LINK CDATA #FIXED "SIMPLE"
HREF CDATA #REQUIRED
TITLE CDATA #IMPLIED>

<!ELEMENT Notes (#PCDATA)>
```

Table 5.

FIG. 3 illustrates a portion of the exemplary EGF pathway including spatial information and determined relationships between entities and transformations from the extracellular EGF signal 90, through the cell membrane 76 via EGF receptor 94, Grb2 96, Sos 98 and inactive Ras 100, and into the cell cytoplasm via active Ras 102.

Method 46 allows a user to dynamically build (or edit) and save information associated with a biological pathway that represents a biological function with determined relationships. Method 46 allows information about a biological entity to be organized into a hierarchy including multiple dimensions of information. Spatial information about each entity or transformation is captured by associating an entity or transformation with a specific cellular component (e.g., cell membrane 76). Varying shapes are used to represent different entities and transformations in a biological pathway.

Displaying experimental information with determined relationships from a local computer

FIG. 7 is a flow diagram illustrating a Method 174 for dynamically displaying experimental information including determined relationships. At Step 176, a biological pathway with determined relationships is selected from a list of biological pathways displayed on a graphical user interface on a computer. At Step 178, a display mode used to display the biological pathway

is selected from the graphical user interface. The display mode allows hierarchical information associated with the selected biological pathway with determined relationships to be displayed on the graphical user interface. At Step 180, a graphical representation of the selected biological pathway with determined relationships is dynamically generated on the graphical user interface using associated information from a database for the selected biological pathway and the selected mode of operation. The graphical representation of the selected biological pathway is not stored in a database, but dynamically generated from information in a database. The selected biological pathway is dynamically generated using a first set of colors to indicate a level of generalization in a multi-dimensional hierarchy used to display individual components of the biological pathway.

Method 174 (FIG. 7) is illustrated with GUI 64 (FIG. 3) with the portion of the cellular Epidermal Growth Factor ("EGF") signaling pathway input and stored using Method 46 (FIG. 2). However, the present invention is not limited to such an embodiment and Method 174 can be used with biological pathways that were input and stored with other methods.

In such an embodiment at Step 176, the EGF biological pathway is selected from a list of biological pathways displayed on a graphical user interface on an internal or local computer 12, 14. The information associated with the biological pathways was stored in a local database using Method 46. In this embodiment, the information associated with the biological pathways includes the multi-dimensional and related information described above for Method 46. In such an embodiment, the list of biological pathways can be displayed by selecting the graphical explore button 84 from the GUI 64.

When the graphical explore button 84 is selected a list of saved biological pathways is displayed for a user. In one embodiment of the present invention, the list of biological pathways is created dynamically from a database. In another embodiment of the present invention, the list of biological pathways is displayed from a static list saved in a database.

At Step 178, a display mode to display the biological pathway is selected from the graphical user interface. The display mode allows hierarchical information associated with the selected biological pathway with determined relationships to be displayed on the graphical user interface. In this specific embodiment, the display mode of operation includes a summary, dimension and a link display mode. However, the present invention is not limited to these display modes and more, fewer or equivalent display modes can also be used. The display modes allow a user to view information associated with an entity or transformation in a hierarchical fashion from general to specific.

The "summary" display mode allows a user to view general multi-dimensional information about a selected entity or transformation in a selected biological pathway (e.g., from hierarchy 114). The summary display mode includes displaying graphical shapes of varying colors and arrows representing a general level for entities and transformations in a biological pathway. Visiting a pre-determined level in the summary mode may automatically switch the user into the dimension mode and/or the link mode.

The "dimension" display mode allows a user to view general or specific multi-dimensional information associated with entities or transformations in a biological pathway (e.g. from hierarchy 126 and 152).

The dimension display mode allows a user to electronically link to other multi-dimensional information stored in the internal databases. In such an embodiment of the present invention, the multi-dimensional information is obtained exclusively from local databases. In another embodiment of the present invention, the multi-dimensional information is obtained from the local databases as well as from the public domain databases.

The "link" display mode allows a user to view related information stored in external databases associated with entities and/or transformations in a biological pathway. In one embodiment of the present invention, related information for the link mode is obtained exclusively from external databases. As a result, the link mode includes use of additional network security features (e.g., logins, passwords, firewalls, encryption, other secure transfer, etc.) to protect the integrity of the private network 16. In other embodiment of the present invention, related information for the link mode is obtained from the external databases and the internal databases. In such an embodiment, all or selected portions of related information from the external databases may be cached in one or more of the internal databases or in random access memory for quicker access and display after any of the related information is accessed once from the external databases.

At Step 178, a graphical representation of the selected EGF biological pathway with determined shapes and arrows is dynamically generated with a first set of colors on the graphical user interface using associated information from the internal database for the selected biological pathway and the selected mode of operation. The first set of colors is used to indicate a level of generalization in a multi-dimensional hierarchy used to display the biological

pathway. The first set of colors may include, for example, red, orange, yellow, green, blue, indigo and violet to indicate a highest level or general level, to a lowest level, or most specific level, in the multi-dimensional hierarchy.

For example, FIG. 3 illustrates a portion of the EGF pathway as displayed in the summary mode. The graphical representation of the EGF pathway as illustrated in FIG. 3 is not stored in a database. That is, shapes 92, 94, 96, 98, 100, 102 and arrows 104, 106, 108, 110, 112 are not stored in a database. Instead an identifier for the shapes and arrows are stored in a database as pathway information (e.g., XCoord, YCoord and Shape indication of a Functional-Unit in the XML DTD from Table 5). When database records are read for a selected biological pathway information in the database records are used to dynamically generate a graphical shape in a desired location that is displayed on the GUI 64 as is illustrated in FIG. 3.

FIG. 8 is a block diagram illustrating an exemplary general multi-dimensional information page 182 that is dynamically created and displayed for a user in the summary display mode. A similar page may be dynamically created and displayed to input general multi-dimensional information. A general multi-dimensional information electronic display page is dynamically created from information in the local databases in a hardware independent mark-up language and displayed for the user.

For example, an electronic display page is created HTML, XML or other hardware independent mark-up languages known in the art. However, virtually any programming language can be used to create and display the electronic display page (e.g., C, C++, Visual Basic, Visual C++, Java, etc.)

and the present invention is not limited to hardware independent mark-up languages.

The general multi-dimensional information page 182 includes a display field for a species 184, an experimental system 186, a functional unit for an entity 188, a transformation 190 and a compartment 192. The contents of these fields were discussed above for the multi-dimensional hierarchy 114 (FIG. 4). The multi-dimensional information page 182 illustrated in FIG. 8 is dynamically created from the exemplary multi-dimensional information input at Step 56 (FIG. 2A) and illustrated in Table 1 above. Such multi-dimension information is created from a hierarchy and/or a directed graph as was discussed above.

The multi-dimensional information page 182 also includes electronic links to other multi-dimensional information. For example, in the functional unit display field 188, the letters "EGF" is underlined indicating an electronic link to additional specific multi-dimensional information for a cell (e.g., from entity hierarchy 126 of FIG. 5).

The summary mode also allows a user to "zoom in" and "zoom out" to view more detailed information associated with an entity or transformation in a selected biological pathway. The zooming is completed by selecting the graphical zoom button 78 on the GUI 64. Zooming to a pre-determined level in the summary mode may automatically switch the user into the dimension mode and/or the link mode. The summary mode also allows a user to pan back and forth on the GUI 64 to view multiple cells displayed on the GUI 64 for a biological pathway that may be inter-cellular. The panning is completed by selecting the graphical pan button 80 on the GUI 64.

FIG. 9 is a block diagram illustrating an exemplary specific multi-dimensional information page 194 for a biological entity such as a cell. This display page can be dynamically displayed by selecting the "MULTI Button" 86 from the GUI 64 (FIG. 3) or by access from another display (e.g., clicking on the word CELL in the functional unit display field 188 (FIG. 8) mode. The multi-dimensional information page 194 includes a display field for a morphology 196, an optional EM photograph 198 and an optional fluorescent view 200. These display fields correspond to the multi-dimensional information from the entity hierarchy 126 (FIG. 5) that was input at Step 56 (FIG. 2A). Such multi-dimension information is created from a hierarchy and/or a directed graph as was discussed above. The multi-dimensional information page 194 also includes display fields for basic information 202, site information 204, functions 206, enzymes 208, if any, reactions 210, a transport system 212, and a pathway view 214.

FIG. 9 illustrates an exemplary specific multi-dimensional information page 194 at an entity level in a multi-dimensional hierarchy that might be displayed in a dimension display mode for extracellular EGF signal 90 on the GUI 64 (FIG. 3). Such multi-dimension information is created from a hierarchy and/or a directed graph as was discussed above. The multi-dimensional information page 194 illustrated in FIG. 9 is dynamically created from the exemplary multi-dimensional information input at Step 56 (FIG. 2A) and illustrated in Table 2 above. Other entities in the EGF pathway would have similar multi-dimensional information pages. Transformations in the EGF pathway would also have similar multi-dimensional information pages dynamically generated and displayed (e.g., based on hierarchy 152).

The specific multi-dimensional information page 194 also includes electronic links to other information. For example, in the basic information display field 202, the letters "EGF" are underlined indicating an electronic link to additional related information in a local database. In this example, selecting the electronic link for EGF would link the user to a three-dimensional graphical display of the EGF signal molecule. The remaining underlined text on the multi-dimensional information page 194 also indicates electronic links to additional information in local databases.

FIG. 10 is a block diagram illustrating an exemplary related information page 216 that is dynamically created and displayed for a user in a link display mode. A related information electronic display page is dynamically created from information in external databases and/or cached in local databases in a hardware independent mark-up language and displayed for the user.

For example, an electronic display page is created in XML, HTML or other hardware independent mark-up languages known in the art. However, virtually any programming language can be used to create and display the electronic display page (e.g., C, C++, Visual Basic, Visual C++, Java, etc.) and the present invention is not limited to hardware independent mark-up languages.

The related information page 216 includes, but is not limited to, a display field for entities 218, assays 220, compounds 222, diseases 224, authors 226, expression 228, validations 230 and other known pathways 232 this entity or transformation participates in.

FIG. 10 illustrates an exemplary related information page 216 that might be displayed in the link mode for extracellular EGF signal 90 on the GUI 64 (FIG. 3). The related information page 216 illustrated in FIG. 10 is dynamically created from the exemplary related information input at Step 58 (FIG. 2A), illustrated in Table 4 above and stored in external databases.

The related information page 216 may also include electronic links to other remote information. Such electronic links are also illustrated with underlined text in FIG. 10. For example, in the authors field 226 the author, SHIGEO TSUCHIYA, is underlined indicating an electronic link to other related works by the same author stored in external databases on a public network like the Internet.

As was discussed above, the link display mode includes use of additional network security features (e.g., logins, passwords, firewalls, encryption, other secure transfer, etc.) to protect the integrity of the private network 16. Selected portions of related information from the external databases may be cached in one or more of the internal databases for quicker access and display after any of the related information is accessed once from the external databases.

Displaying experimental information with determined relationships from a remote computer

The present invention has been described with respect to use from internal or local computers 12,14 on private LAN 16. In such an embodiments, information associated with a biological pathway with determined relationships may be stored in a local proprietary database 18, 20

without public access. Such information may be used for private research and may never be made available to the public.

In another embodiment, information associated with a biological pathway with determined relationships may be stored in a local database with a public access portion 24, 26. Such information may be made available to the public when the research used to generate the information is at a stage appropriate for public review or public disclosure. Such information can be used to quickly make the new research information available to a large number of people via the public network 28 for critical review.

However, the present invention can also be used from external computers 30, 32, 34, 36 via public network 28 to input and/or access and display information from a private organization. For example, Method 46 (FIG. 2) may be used from external computers 30, 32, 34, 36, to input and/or edit a biological pathway with determined relationships that can immediately be shared by a large number of people via the public network 28.

In such an embodiment, any information associated with a biological pathway with determined relationships may be temporarily stored in a local database associated with the external computers (not illustrated in FIG. 1) and then transferred to the internal databases with public access 24, 26 on the private LAN 16. The information may also be transferred directly to the internal databases with public access 24, 26 on the private LAN 16 as the information is input. Related information may also be transferred to one or more of the plural public domain databases 38, 40, 42, indirectly or directly. An organization that owns the private intranet LAN 16 may designate its internal databases with public access 24, 26 as an information repository and

allow members of the public to input, access, display and share such information to aid and further advance biological research on a world-wide basis.

FIG. 11 is a flow diagram illustrating a Method 234 for dynamically displaying experimental information including determined relationships displaying from a remote computer. At Step 236, a request is made on a graphical user interface on remote computer connected to a public network, to select a biological pathway with determined relationships from a private database server connected a private network. The private network includes plural private databases with public access including information associated with plural of biological pathways with determined relationships. At Step 238, a display mode is selected to display the biological pathway with determined relationship from the graphical user interface on the remote computer. The display modes allows hierarchical information associated with the biological pathway with determined relationships to be displayed on the graphical user interface. At Step 240, a first portion of information associated with the selected biological pathway with determined relationships is received from the plural private databases via the private database server on the private network in a hardware independent mark-up language on the remote computer. At Step 242, a second portion of information associated with the selected biological pathway with determined relationships from plural public databases via one or more public database servers on the public network. At Step 244, a graphical representation of the selected biological pathway with determined relationships is dynamically generated on the graphical user interface on the remote computer using the selected display mode, the first

portion of information from the private network and the second portion of information from the public network, thereby creating a graphical representation of the selected biological pathway with determined relationships with information from a plurality of private databases and with information from a plurality of public databases.

Method 232 (FIG. 11) is illustrated with a specific example from remote computer 30 including GUI 64 (FIG. 3). However, the present invention is not limited to this specific example virtually any biological pathway can be input, displayed and manipulated from a remote computer using Method 232 and GUI 64.

In such an embodiment, at Step 234 a request is made on the GUI 64 on the remote computer 30 connected to the Internet 28, to select a biological pathway (e.g., the EGF signaling pathway) with determined relationships from a private database server 22 connected a private intranet LAN 16. The selection includes inputting a new biological or requesting a previously saved biological pathway with determined relationships. At Step 236, a display mode is selected to display the biological pathway from the GUI 64 on the remote computer 30. The display mode includes the summary, dimension and link display modes described above. However, other display modes can also be used on the present invention is not limited to these display modes.

Step 238, a first portion of information associated with the selected biological pathway is received from the plural private databases 24, 26 via the private database server 22 on the private intranet LAN 16 in a hardware independent mark-up language on the remote computer. The first portion of information includes information in XML, HTML or other hardware

independent mark-up languages. At Step 240, a second portion of information associated with the selected biological pathway with determined relationships from plural public databases 38, 40, 42 via one or more public database servers on the Internet 28. The second portion of information also includes information in XML, HTML or other hardware independent mark-up languages.

In one embodiment of the present invention, the first portion of information includes the XML conforming to the DTD illustrated in Table 5. The second portion of the information includes XML data (e.g., electronic links or actual information) that are used with the XML DTD to dynamically generate the biological pathway and related information.

In another embodiment of the present invention, the first portion of information and the second portion of information each include discrete XML data that is combined and used to dynamically generate a graphical representation of the selected biological pathway with determined relationships. However, other types of data can also be used for the first portion and the second portion of information, and the present invention is not limited to the XML data described.

At Step 242, a graphical representation of the selected biological pathway with determined relationships is dynamically generated on the GUI 64 on the remote computer 30 using the selected display mode, the first portion of information from the private intranet LAN 16 and the second portion of information from the Internet 28. This creates a graphical representation of the selected biological pathway with determined

relationships with information from a plural private databases 24, 26 and with information from a plural public databases 38, 40, 42.

In one embodiment of the present invention, the first portion of information includes general and/or multi-dimensional information (e.g., FIGS. 8 and 9) for a biological entity or a transformation is stored in the plurality of private databases 24, 26 on the private network 16. The second portion of information includes related information (e.g., FIG. 10) for a biological entity or transformation is stored in the plural public databases 38, 40, 42, on the public network 28. The second portion of the information may include electronic links to related information or actual electronic information.

In one embodiment of the present invention, Step 242 includes dynamically generating the graphical representation of the selected biological pathway with a first set of colors on the GUI 64 on the remote computer 30. As was described above, the first set of colors is used to indicate a level of generalization in a hierarchy or directed graph used to display the biological pathway on the GUI 64.

The graphical representation of the selected biological pathway is generated "seamlessly" so a user is not able to visually determine by observing the selected biological pathway that information used to create it came from plural databases on private and public networks.

A user on a remote computer can also input and/or modify information and/or dynamically generate a selected biological pathway with Method 46 (FIG. 2) or Method 232 (FIG. 11). In such an embodiment, a request is received to change the selected biological pathway with determined relationships. Any changes relating to the first portion of information used to

display the selected biological pathway is sent to the private database server 22 on the private network 16 to update appropriate private databases in the plural local databases 24,26 on the private network 16. Any changes relating to the second portion of information used to display the selected biological pathway is sent to an appropriate public database server on the public network 28 to update appropriate public databases in the plural databases 38, 40, 42, on the public network 28. In one embodiment of the present invention, only changes to the first portion of the information is allowed. In another embodiment, only changes to the second portion of the information is allowed. In another embodiment of the present invention, changes to both the first portion and the second portion of information are allowed.

The methods and system described herein may provide at least the following advantages. An input/edit tool (e.g., GUI 64) is provided to input/edit a biological pathway with determined relationships using predefined entities and transformation templates (e.g., shapes and arrows) to capture information about that pathway as it is drawn. Spatial information about entities and transformations is captured by associating an entities and transformations with specific biological compartments. Graphical biological pathway diagrams are dynamically generated to represent biological functions.

A navigation tool (e.g., GUI 64) is provided to retrieve information associated with selected biological entities or transformations from local and remote databases. Information is presented hierarchically, from more general to more specific. Color-coding is used to reflect levels of generalization. Entity and transformation information is organized into hierarchical dimensions. Users can selectively expand and/or collapse parts of the

graphical pathway, or rearrange the layout of the pathway. The methods and system may also be used to provide new bioinformatic techniques used to make observations about biological pathways, such as cell pathways, with determined relationships.

It should be understood that the programs, processes, methods and systems described herein are not related or limited to any particular type of computer or network system (hardware or software), unless indicated otherwise. Various types of general purpose or specialized computer systems may be used with or perform operations in accordance with the teachings described herein.

In view of the wide variety of embodiments to which the principles of the present invention can be applied, it should be understood that the illustrated embodiments are exemplary only, and should not be taken as limiting the scope of the present invention.

For example, the steps of the flow diagrams may be taken in sequences other than those described, and more or fewer elements may be used in the block diagrams. While various elements of the preferred embodiments have been described as being implemented in software, in other embodiments in hardware or firmware implementations may alternatively be used, and vice-versa.

The claims should not be read as limited to the described order or elements unless stated to that effect. Therefore, all embodiments that come within the scope and spirit of the following claims and equivalents thereto are claimed as the invention.

WE CLAIM:

1. A method for storing experimental information with determined relationships, comprising:

(a) selecting a shape from a menu on graphical user interface on a computer, wherein the shape represents an entity that participates in a biological pathway;

(b) placing the shape at a desired location in an electronic window on the graphical user interface;

(c) selecting an arrow from the graphical user interface, wherein the arrow represents a transformation between entities that participate in a pathway;

(d) connecting the arrow and the shape, thereby providing a graphical representation of a transformation of an entity with a determined relationship;

(e) inputting multi-dimensional information, to link the shape and arrow to multi-dimensional information specifying the entity and the transformation wherein the multi-dimensional information is stored in a database;

(f) inputting related information, if any, to link the shape and arrow to other information related to the entity and transformation from a plurality of external databases;

(g) repeating steps (a)-(f) a desired number of times; and

(h) saving information associated with a plurality of shapes connected with a plurality of arrows as a biological pathway with determined relationships in a database, wherein the biological pathway defines a

hierarchical representation of a biological function with determined relationships between the entities and transformations.

2. A computer readable medium having stored therein instructions for causing a central processing unit to execute the method of Claim 1.

3. The method of Claim 1 wherein the shape represents biological entities including a sub-component of a cell, a cell or an aggregation of a plurality of cells.

4. The method of Claim 3 wherein biological entities include active entities, inactive entities, entity inhibitors, factors exchanged between entities or intermediate entity transformation products.

5. The method of Claim 1 wherein the arrow represents a biological transformation between a first entity and a second entity.

6. The method of Claim 5 wherein the biological transformation includes a transcription factor activation, cellular hypertrophy, protein kinase activation, protease activation, gene expression, receptor activation, apoptosis, internalization of cell surface receptor proteins, mitochondrial potential, neurite outgrowth, cell viability or miotic index for a sub-component of a cell, a cell or an aggregation of a plurality of cells.

7. The method of Claim 1 wherein step (e) includes inputting multi-dimensional information for a species, experimental system, functional types to classify an entity, transformation types to classify a transformation, or a compartment where an entity or transformation occurs.

8. The method of Claim 7 further includes inputting multi-dimensional information for a biological entity including, a component view, a morphology of the biological entity, an optional electron microscope photograph of the biological entity, an optional fluorescent view of the biological entity, basic information, site information, function information, enzyme information, if any, reaction information, transport system information or a pathway view.

9. The method of Claim 8 further comprising inputting multi-dimensional information for a tissue, organ, system, or organism.

10. The method of Claim 1 wherein step (f) includes specifying related information, if any, including information about entities including assays, including an experimental protocol used to test a selected entity or transformation; compounds, including compounds that are effective on selected entities or transformations; diseases, including known diseases that are related to the selected shapes or arrows; authors, including other authors who have expertise in the selected entities or transformations; expressions,

including gene expression data related to the selected entity or transformation, validation, including a level of credibility of the existence and role of the selected entity or transformation; or pathways, including other pathways that the selected entities or transformations participate in.

11. The method of Claim 1 wherein step (h) includes saving information associated with a plurality of shapes connected with a plurality of arrows as a biological pathway with determined relationships in an electronic document in a database in a hardware independent mark-up language.

12. The method of Claim 11 wherein the hardware independent mark-up language is the Extensible Mark-Up Language ("XML") or the HyperText Markup Language("HTML").

13. The method of Claim 11 wherein the electronic document conforms to an Extensible Markup Language Document Type Definition.

14. The method of Claim 1 wherein step (b) includes placing a shape with a first color in an electronic window on the graphical user interface, wherein the first color indicates that no multi-dimensional or related information has input for the shape.

15. The method of Claim 1 wherein step (e) includes changing a first color used to display the shape to a second color after the multi-dimensional information has been input, thereby allowing a user to visually determine whether any multi-dimensional information has been input for the shape.

16. The method of Claim 1 wherein step (f) includes changing a second color used to display the shape after multi-dimensional information has been input at step (e) to a third color after the related information has been input for the shape, thereby allowing a user to visually determine whether both multi-dimensional and related information have both been input for the shape.

17. A method for displaying experimental information with determined relationships, comprising:

selecting a biological pathway with determined relationships from a list of biological pathways displayed on a graphical user interface on a computer, wherein information associated with the biological pathways is stored in a database;

selecting a display mode used to display the biological pathway from the graphical user interface, wherein the display mode allows hierarchical information associated with the selected biological pathway with determined relationships to be displayed on the graphical user interface; and

dynamically generating a graphical representation of the selected biological pathway with determined relationships on the graphical user interface on the local computer using information from the internal database and the selected display mode with a first set of colors, wherein the first set of

colors are used to indicate a level of generalization in a hierarchy or a directed graph used to display individual components of the biological pathway.

18. A computer readable medium having stored therein instructions for causing a central processing unit to execute the method of Claim 17.

19. The method of Claim 17 wherein the step of selecting a display mode of operation used to display the biological pathway includes selecting a summary, dimension or link display mode.

20. The method of Claim 19 wherein the summary display mode includes displaying graphical shapes and arrows of varying colors representing entities and transformations in a biological pathway.

21. The method of Claim 19 wherein the dimension display mode includes displaying multi-dimensional information associated with a biological pathway and allows a user to electronically link to other multi-dimensional information in a plurality of local databases.

22. The method of Claim 19 wherein the link display mode includes displaying related information stored in external databases associated with entities or transformations in a biological pathway and includes using security features to access related information stored in external databases.

23. The method of Claim 22 wherein the security features includes using a login, password, firewall or encryption.

24. The method of Claim 17 wherein the first set of colors used to indicate a level of generalization in a multi-dimensional hierarchy used for individual components of the biological pathway include using the colors red, orange, yellow, green, blue, indigo and violet to indicate a highest level, or more general level, to a lowest level, or more specific level, of generalization in the multi-dimensional hierarchy.

25. The method of Claim 17 further comprising:

receiving a selection input to jump from a higher level to a lower level in a multi-dimensional hierarchy, thereby selectively expanding a portion of the biological pathway from a display of general information to a display of more specific information; and

creating dynamically appropriate information for the lower level on the graphical user interface in a new color different from the higher level, wherein the new color represents a lower, more specific, level in the multi-dimensional hierarchy.

26. The method of Claim 25 further comprising;

recording a history of any selection inputs to allow a user to determine what selection inputs were completed; and

displaying a graphical representation of the history in the multi-dimensional hierarchy, thereby allowing a user to visually determine how the multi-dimensional hierarchy was navigated.

27. The method of Claim 25 further comprising:

receiving a selection input to jump from a lower level to a higher level in the multi-dimensional hierarchy, thereby selectively collapsing a portion of the biological pathway from a display of more specific information to a display of more general information; and

creating dynamically appropriate information for the higher level on the graphical user interface in a new color different from the lower level, wherein the new color represents a higher level in the multi-dimensional hierarchy.

28. The method of claim 25 wherein the multi-dimensional hierarchy includes a directed graph.

29. A method for displaying experimental information with determined relationships from a remote computer, comprising:

requesting on a graphical user interface on a remote computer connected to a public network, a selected biological pathway with determined

relationships from a private database server connected a private network, wherein the private network includes a plurality of private databases with information associated with a plurality of biological pathways with determined relationships;

selecting a display mode used to display the biological pathway from the graphical user interface on the remote computer, wherein the display mode allows hierarchical information associated with the selected biological pathway with determined relationships to be displayed on the graphical user interface;

receiving a first portion of information associated with the selected biological pathway with determined relationships from the plurality of private databases via the private database server on the private network in a hardware independent mark-up language on the remote computer;

receiving a second portion of information associated with the selected biological pathway with determined relationships from a plurality of public databases via one or more public database servers on the public network;

dynamically generating a graphical representation of the selected biological pathway with determined relationships on the graphical user interface on the remote computer using the selected display mode, the first portion of information from the private network and the second portion of information from the public network, thereby creating a graphical representation of the selected biological pathway with determined relationships with information from a plurality of private databases and with information from a plurality of public databases.

30. A computer readable medium having stored therein instructions for causing a central processing unit to execute the method of Claim 29.

31. The method of Claim 29 further comprising:

receiving a request to change the selected biological pathway with determined relationships;

sending any changes relating to the first portion of information used to display the selected biological pathway with determined relationships to the private database server on the private network to update appropriate private databases from the plurality of local databases on the private network; and

sending any changes relating to the second portion of information used to display the selected biological pathway with determined relationships to an appropriate public database server on the public network to update appropriate public databases from the plurality of databases on the public network.

32. The method of Claim 29 wherein the public network is the Internet and wherein the private network is an intranet.

33. The method of Claim 29 wherein the first portion of information includes multi-dimensional information for a biological entity or a transformation stored in the plurality of private databases on the private network.

34. The method of Claim 29 wherein the second portion of information includes related information for a biological entity or transformation stored in the plurality of public databases on the public network.

35. The method of Claim 29 wherein the second portion of information includes electronic links to related information instead of actual related information.

36. A system for dynamically storing, retrieving and displaying of experimental information with determined relationships, comprising in combination:

a graphical user interface for dynamically inputting or editing information associated with biological pathway with determined relationships using shapes and arrows to represent entities and transformations to capture information associated with biological pathway as it is drawn, for saving information associated with a biological pathway in a database, for retrieving information associated with selected biological entities or transformations from a database, for dynamically generating graphical representation of a biological pathway with a plurality of colors from information retrieved from a database, wherein a generated biological pathway includes a hierarchy of associated information, and for navigating through a hierarchy of information associated with a generated biological pathway; and

a database for saving information associated with a plurality of shapes connected with a plurality of arrows as a biological pathway with

determined relationships, wherein the biological pathway defines a hierarchical representation of a biological function with determined relationships between the entities and transformations.

FIG. 1

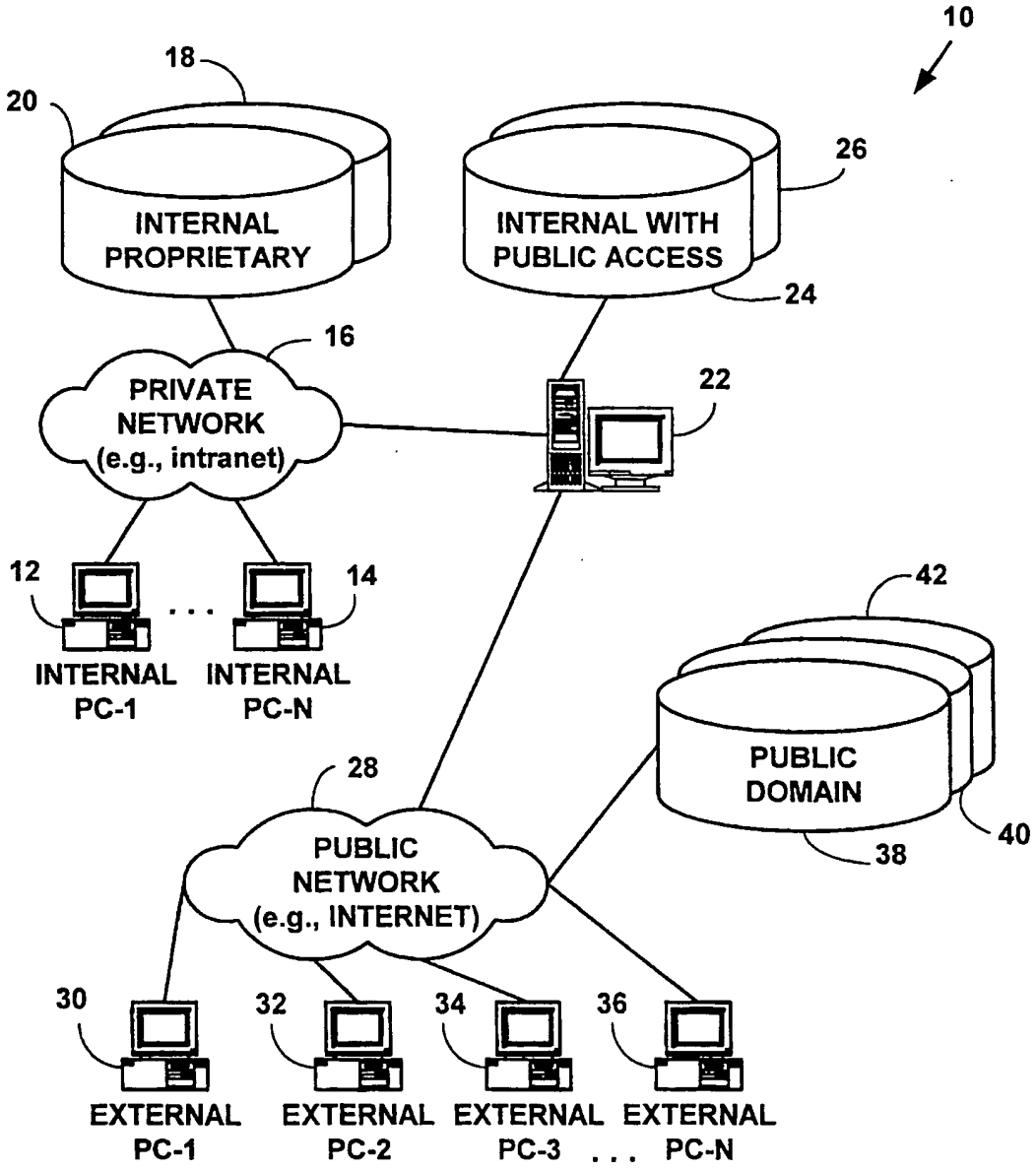

10
18
20
INTERNAL PROPRIETARY
INTERNAL WITH PUBLIC ACCESS
26
24
16
PRIVATE NETWORK (e.g., intranet)
22
12
14
INTERNAL PC-1
INTERNAL PC-N
42
PUBLIC DOMAIN
40
38
28
PUBLIC NETWORK (e.g., INTERNET)
30
32
34
36
EXTERNAL PC-1
EXTERNAL PC-2
EXTERNAL PC-3
EXTERNAL PC-N

FIG. 2A

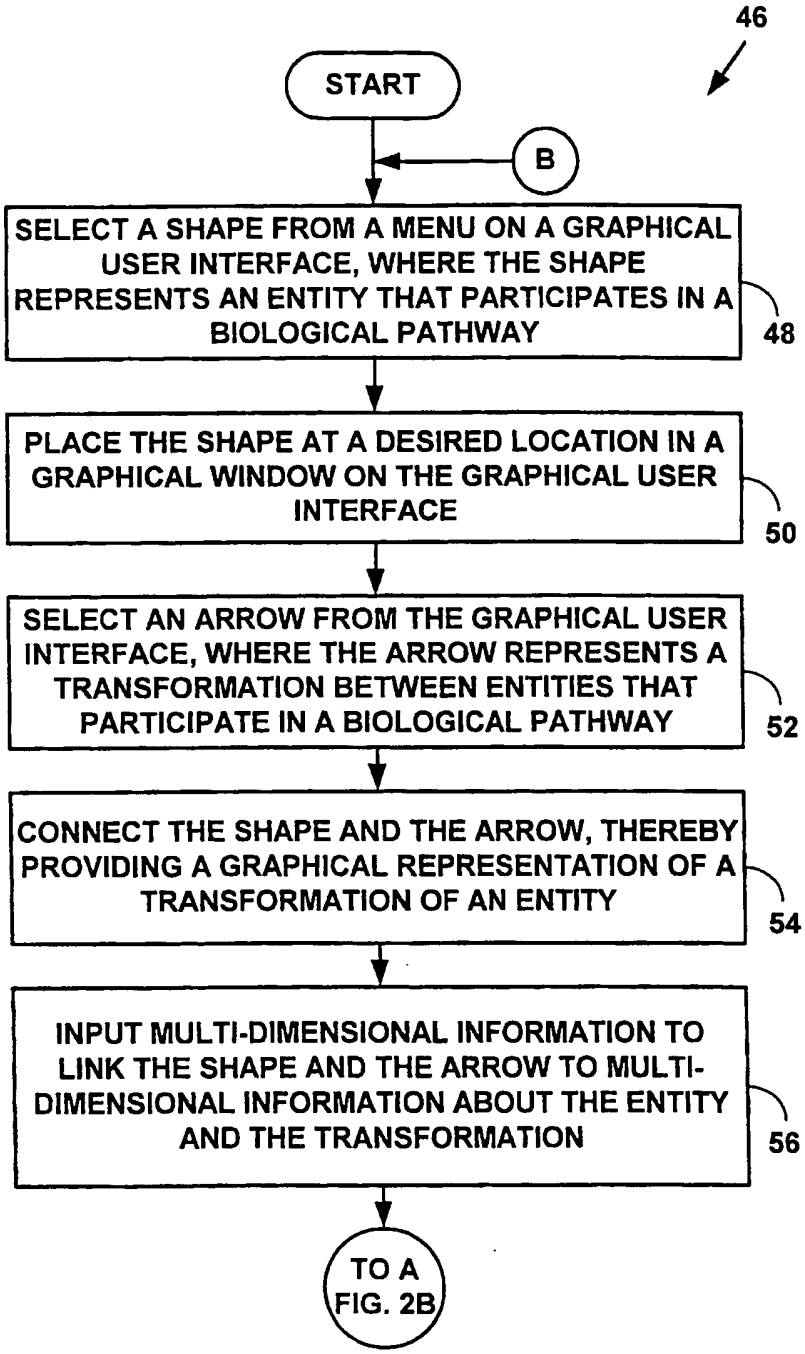

46
START
B
SELECT A SHAPE FROM A MENU ON A GRAPHICAL USER INTERFACE, WHERE THE SHAPE REPRESENTS AN ENTITY THAT PARTICIPATES IN A BIOLOGICAL PATHWAY
48
PLACE THE SHAPE AT A DESIRED LOCATION IN A GRAPHICAL WINDOW ON THE GRAPHICAL USER INTERFACE
50
SELECT AN ARROW FROM THE GRAPHICAL USER INTERFACE, WHERE THE ARROW REPRESENTS A TRANSFORMATION BETWEEN ENTITIES THAT PARTICIPATE IN A BIOLOGICAL PATHWAY
52
CONNECT THE SHAPE AND THE ARROW, THEREBY PROVIDING A GRAPHICAL REPRESENTATION OF A TRANSFORMATION OF AN ENTITY
54
INPUT MULTI-DIMENSIONAL INFORMATION TO LINK THE SHAPE AND THE ARROW TO MULTI-DIMENSIONAL INFORMATION ABOUT THE ENTITY AND THE TRANSFORMATION
56
TO A FIG. 2B

FIG. 2B

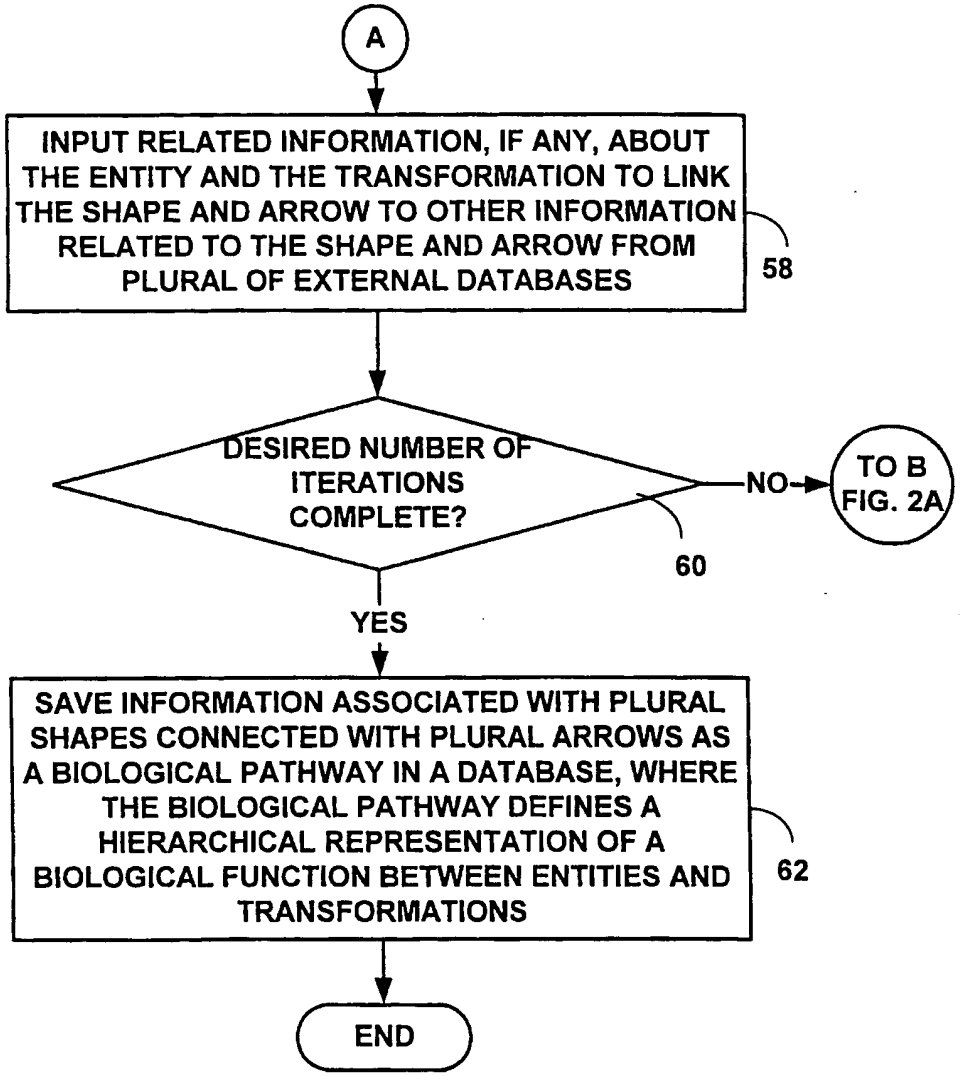

A
INPUT RELATED INFORMATION, IF ANY, ABOUT THE ENTITY AND THE TRANSFORMATION TO LINK THE SHAPE AND ARROW TO OTHER INFORMATION RELATED TO THE SHAPE AND ARROW FROM PLURAL OF EXTERNAL DATABASES
58
DESIRED NUMBER OF ITERATIONS COMPLETE?
60
NO
TO B FIG. 2A
YES
SAVE INFORMATION ASSOCIATED WITH PLURAL SHAPES CONNECTED WITH PLURAL ARROWS AS A BIOLOGICAL PATHWAY IN A DATABASE, WHERE THE BIOLOGICAL PATHWAY DEFINES A HIERARCHICAL REPRESENTATION OF A BIOLOGICAL FUNCTION BETWEEN ENTITIES AND TRANSFORMATIONS
62
END

FIG. 3

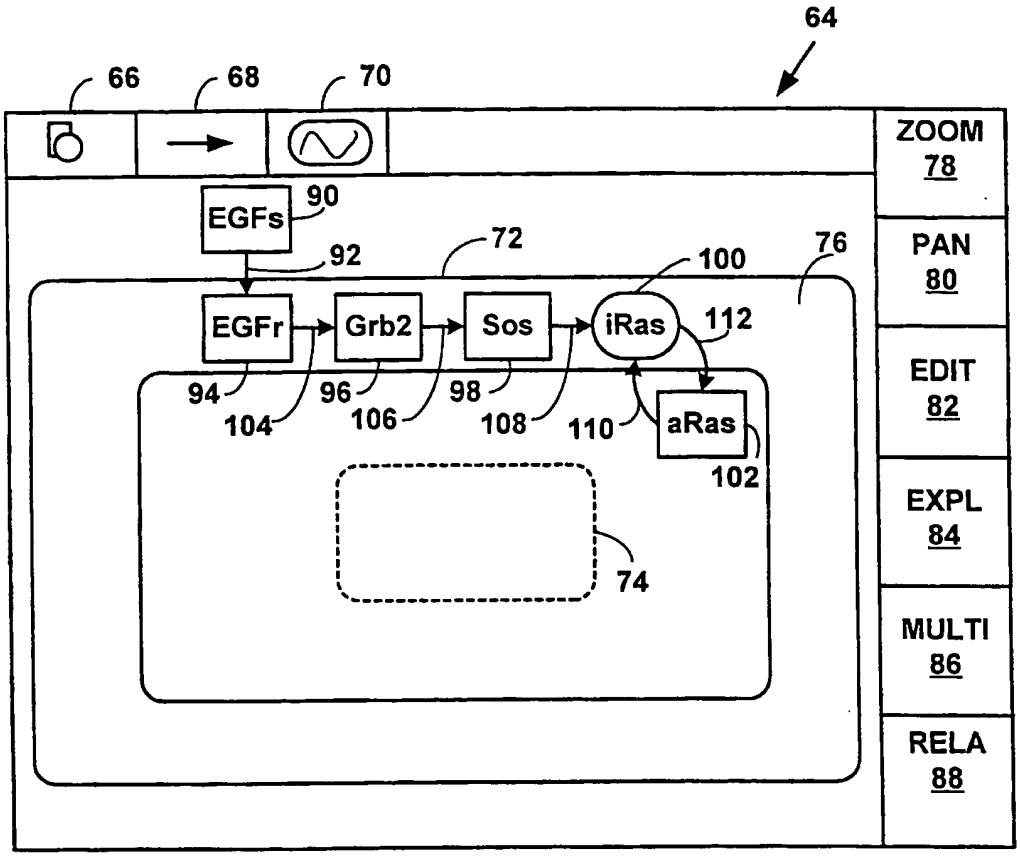

64
66
68
70
ZOOM
78
PAN
80
EDIT
82
EXPL
84
MULTI
86
RELA
88
EGFs
90
92
72
76
100
EGFr
Grb2
Sos
iRas
112
94
96
98
104
106
108
110
aRas
102
74

FIG. 4

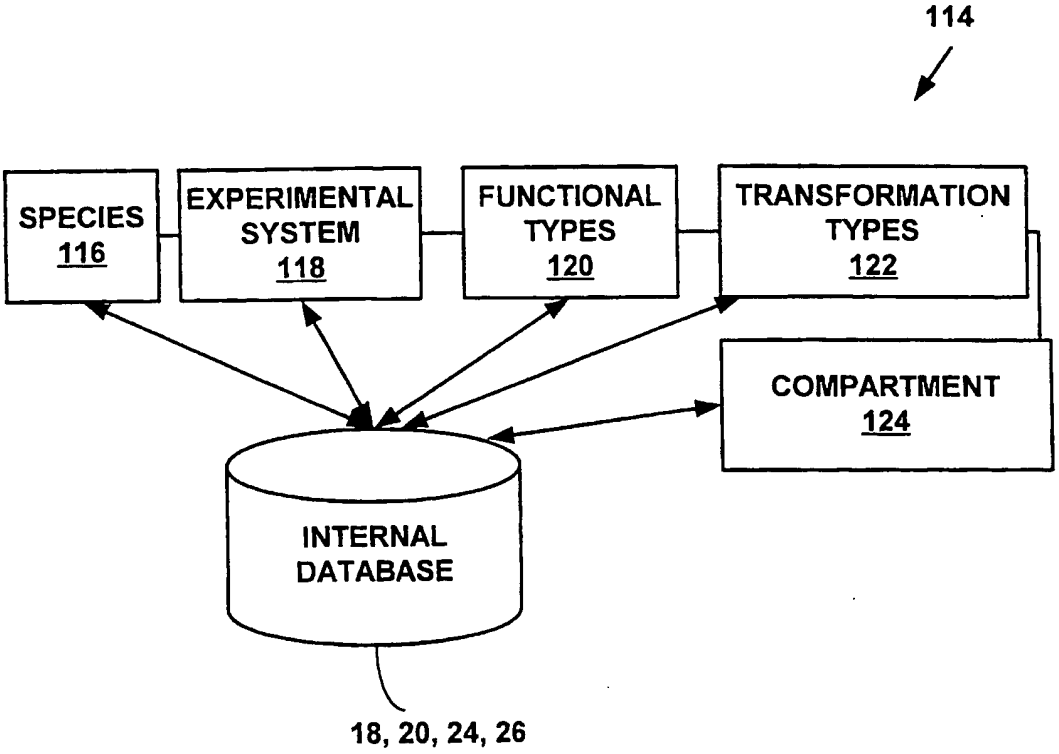

114
SPECIES
116
EXPERIMENTAL
SYSTEM
118
FUNCTIONAL
TYPES
120
TRANSFORMATION
TYPES
122
COMPARTMENT
124
INTERNAL
DATABASE
18, 20, 24, 26

FIG. 5

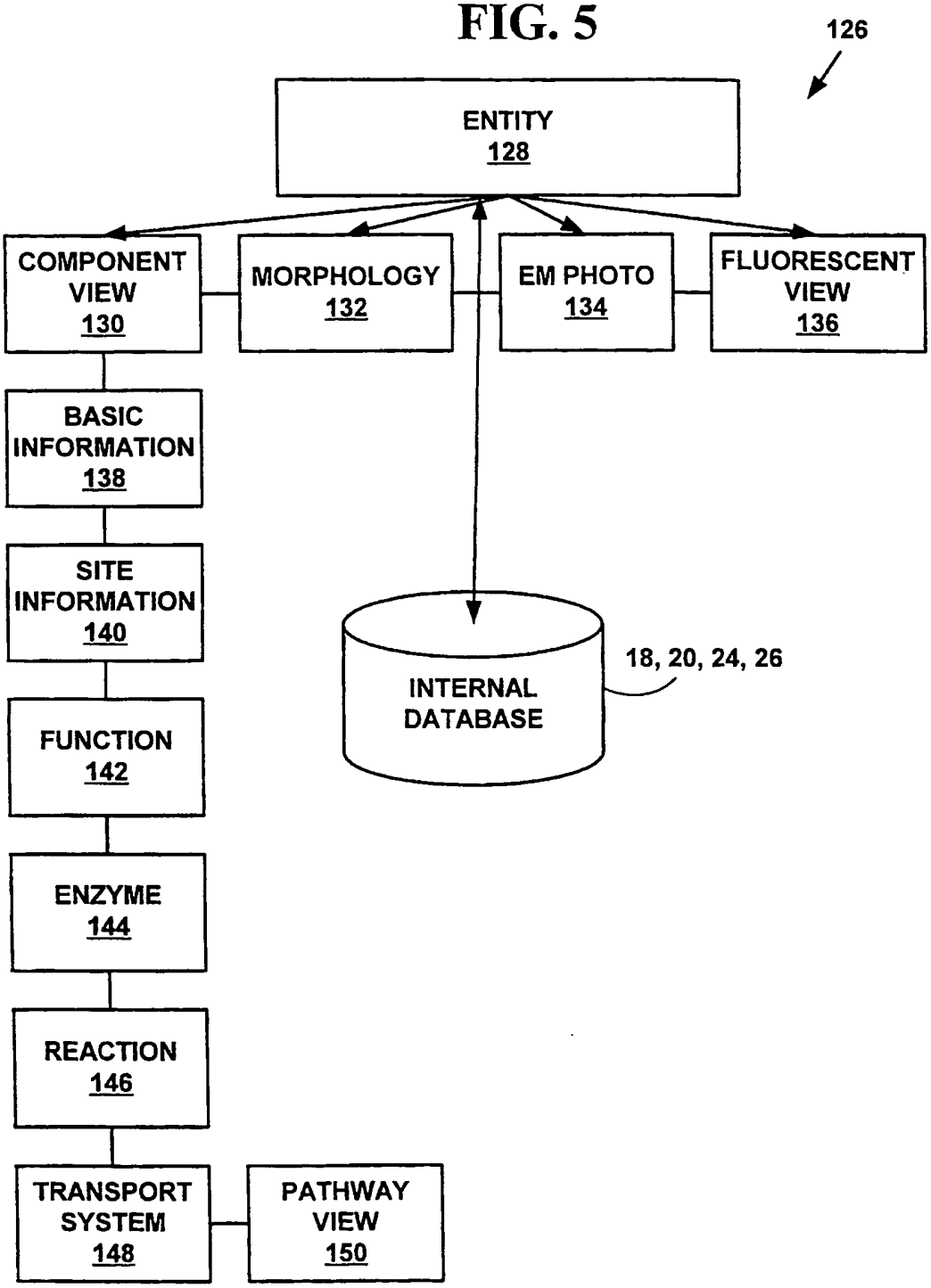

126
ENTITY
128
COMPONENT VIEW
130
MORPHOLOGY
132
EM PHOTO
134
FLUORESCENT VIEW
136
BASIC INFORMATION
138
SITE INFORMATION
140
FUNCTION
142
ENZYME
144
REACTION
146
TRANSPORT SYSTEM
148
PATHWAY VIEW
150
INTERNAL DATABASE
18, 20, 24, 26

FIG. 6

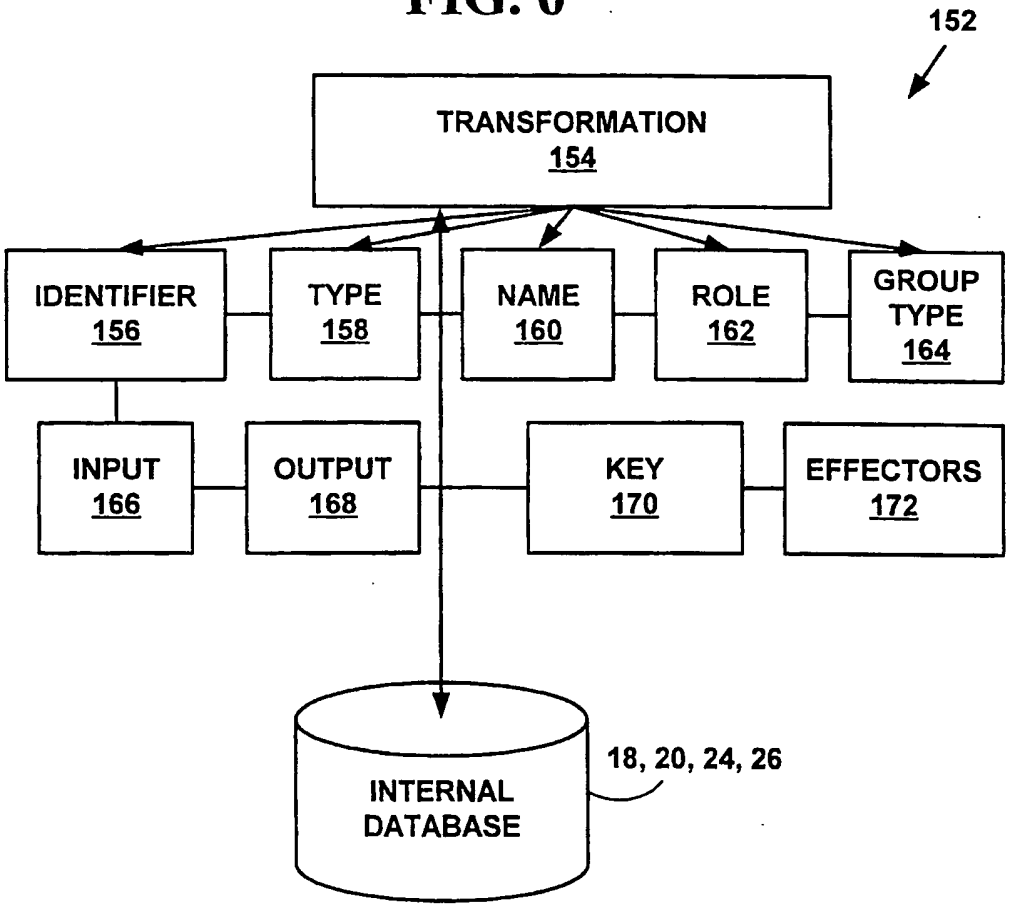

152
TRANSFORMATION
154
IDENTIFIER
156
TYPE
158
NAME
160
ROLE
162
GROUP
TYPE
164
INPUT
166
OUTPUT
168
KEY
170
EFFECTORS
172
INTERNAL
DATABASE
18, 20, 24, 26

FIG. 7

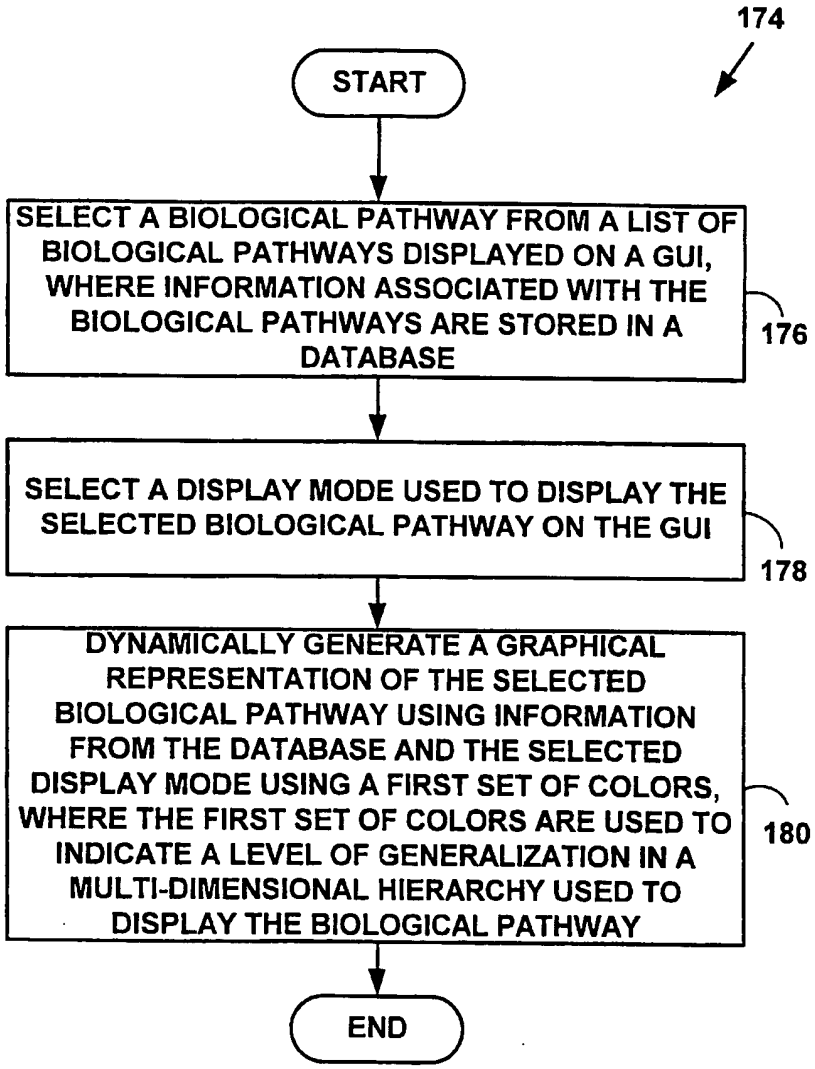

174
START
SELECT A BIOLOGICAL PATHWAY FROM A LIST OF BIOLOGICAL PATHWAYS DISPLAYED ON A GUI, WHERE INFORMATION ASSOCIATED WITH THE BIOLOGICAL PATHWAYS ARE STORED IN A DATABASE
176
SELECT A DISPLAY MODE USED TO DISPLAY THE SELECTED BIOLOGICAL PATHWAY ON THE GUI
178
DYNAMICALLY GENERATE A GRAPHICAL REPRESENTATION OF THE SELECTED BIOLOGICAL PATHWAY USING INFORMATION FROM THE DATABASE AND THE SELECTED DISPLAY MODE USING A FIRST SET OF COLORS, WHERE THE FIRST SET OF COLORS ARE USED TO INDICATE A LEVEL OF GENERALIZATION IN A MULTI-DIMENSIONAL HIERARCHY USED TO DISPLAY THE BIOLOGICAL PATHWAY
180
END

FIG. 8

182

SPECIES 184	HUMAN
EXPERIMENTAL SYSTEM 186	SKELETAL MUSCLE
FUNCTIONAL UNIT 188	EGF, EGF RECEPTOR
TRANSFORMATION 190	EGF BINDING TO EGF RECEPTOR
COMPARTMENT 192	CELL MEMBRANE

FIG. 9

194

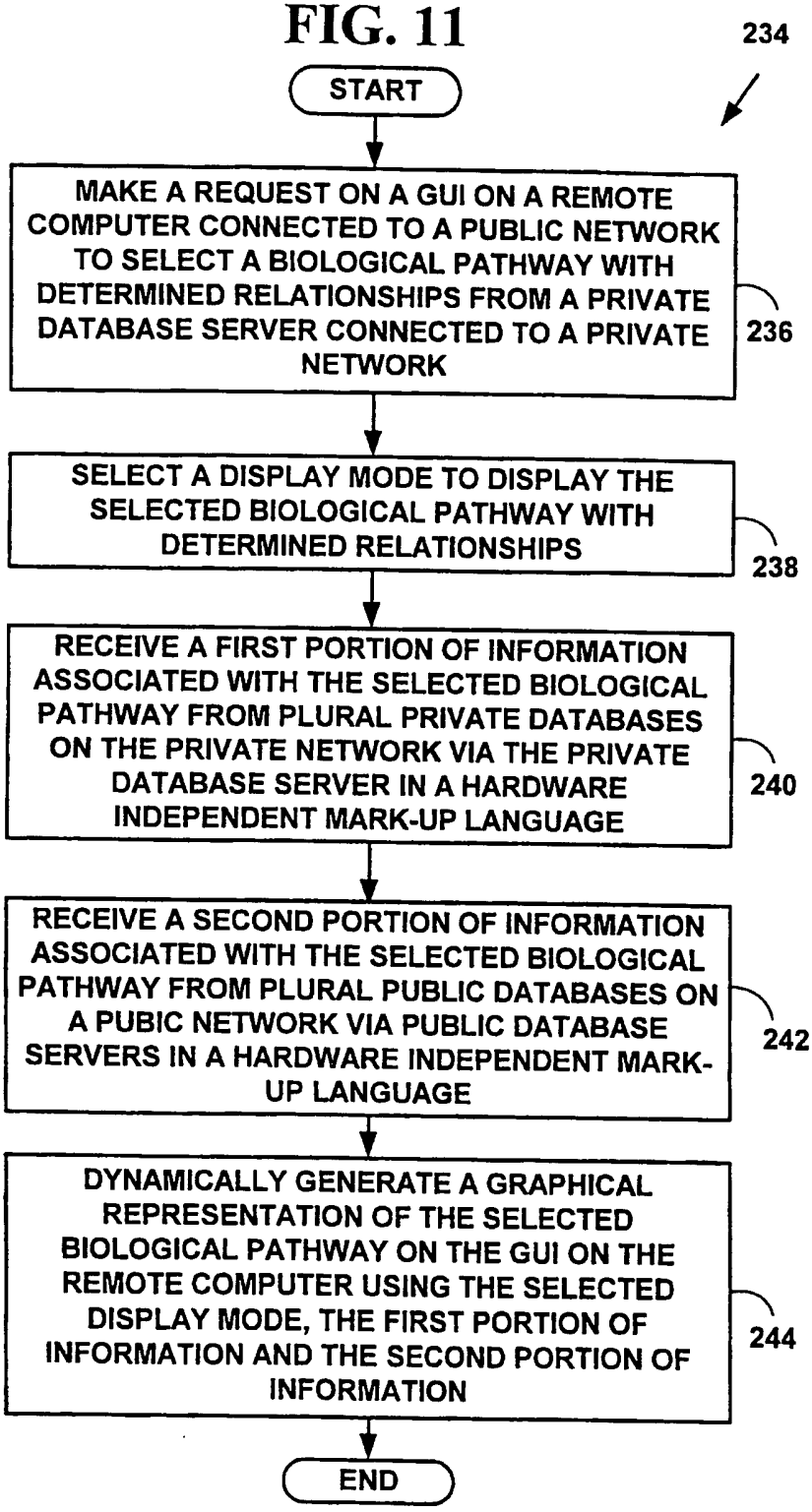
MORPHOLOGY 196	EM PHOTO 198	FLUORESCENT 200
BASIC INFORMATION 202	EGF IS A GLOBULAR PROTEIN OF 6.4 kDa COMPRISING 53 AMINO ACIDS. IT INCLUDES THREE INTRAMOLECULAR DISULFIDE BOND ESSENTIAL FOR BIOLOGICAL ACTIVITY.	
SITE 204	EXTRA CELLULAR SIGNAL MOLECULE	
FUNCTION 206	ACTIVATES ENCODING OF AN INTRINSIC TYROSINE-SPECIFIC PROTEIN KINASE ACTIVITY. THIS KINASE CATALYSES THE TRANSFER OF THE GAMMA-PHOSPHATE OF ATP TO A TYROSINE RESIDUE OF THE RECEPTOR AND ALSO OF SOME OTHER INTRACELLULAR PROTEINS.	
ENZYME 208	TYROSINE-SPECIFIC PROTEIN KINASE	
REACTIONS 210	THE EGF PRECURSOR IS N-GLYCOSYLATED AND CONTAINS A HYDROPHOBIC DOMAIN ALLOWING IT TO BE ANCHORED IN THE PLASMA MEMBRANE. IN CELLS THAT DO NOT CLEAVE THIS PRECURSOR (e.g., KIDNEY CELLS), THE MEMBRANE-BOUND FORM OF THE PRECURSOR MAY ITSELF SERVE AS A RECEPTOR FOR AS YET UNKNOWN LIGANDS. EGF MAY BE INVOLVED ALSO IN JUXTACRINE GROWTH CONTROL MECHANISMS.	
TRANSPORT SYS 212		
PATHWAY 214		

FIG. 10

216

RELATED INFORMATION FOR EGF SIGNALING MOLECULE 218	
ASSAYS 220	CELLOMICS HIGH CONTENT SCREENING EGF ASSAY
COMPOUNDS 222	NA
DISEASES 224	HUMAN CANCERS
AUTHORS 226	SHIGEO TSUCHIYA, et al., SOLUTION STRUCTURE OF SH2 DOMAIN OF Grb2/Ash COMPLEXED WITH EGF RECEPTOR-DERIVED PHOSPHOTYROSINE-CONTAINING PEPTIDE, J. BIOCHEM 125, 1151-1159 (1999).
EXPRESSION 228	NA
VALIDATIONS 230	10
OTHER PATHWAYS 232	PDGF

FIG. 11


234
START
MAKE A REQUEST ON A GUI ON A REMOTE COMPUTER CONNECTED TO A PUBLIC NETWORK TO SELECT A BIOLOGICAL PATHWAY WITH DETERMINED RELATIONSHIPS FROM A PRIVATE DATABASE SERVER CONNECTED TO A PRIVATE NETWORK
236
SELECT A DISPLAY MODE TO DISPLAY THE SELECTED BIOLOGICAL PATHWAY WITH DETERMINED RELATIONSHIPS
238
RECEIVE A FIRST PORTION OF INFORMATION ASSOCIATED WITH THE SELECTED BIOLOGICAL PATHWAY FROM PLURAL PRIVATE DATABASES ON THE PRIVATE NETWORK VIA THE PRIVATE DATABASE SERVER IN A HARDWARE INDEPENDENT MARK-UP LANGUAGE
240
RECEIVE A SECOND PORTION OF INFORMATION ASSOCIATED WITH THE SELECTED BIOLOGICAL PATHWAY FROM PLURAL PUBLIC DATABASES ON A PUBIC NETWORK VIA PUBLIC DATABASE SERVERS IN A HARDWARE INDEPENDENT MARK-UP LANGUAGE
242
DYNAMICALLY GENERATE A GRAPHICAL REPRESENTATION OF THE SELECTED BIOLOGICAL PATHWAY ON THE GUI ON THE REMOTE COMPUTER USING THE SELECTED DISPLAY MODE, THE FIRST PORTION OF INFORMATION AND THE SECOND PORTION OF INFORMATION
244
END

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 00/04331

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G06F17/50 G06F17/30 G06F19/00 //G06F159:00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, COMPENDEX, BIOSIS, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SALAMONSEN W ET AL: "BioJAKE: a tool for the creation, visualization and manipulation of metabolic pathways" PACIFIC SYMPOSIUM ON BIOCOMPUTING '99, PROCEEDINGS OF THE PACIFIC SYMPOSIUM ON BIOCOMPUTING '99, MAUNA LANI, HI, USA, 4-9 JAN. 1999, pages 392-400, XP002143430 1999, Singapore, World Scientific, Singapore ISBN: 981-02-3624-7 the whole document	1-30, 32-36

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2000	07/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fournier, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 00/04331

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 22575 A (INTERTECH VENTURES LTD ;THALHAMMER REYERO CRISTINA (US)) 25 July 1996 (1996-07-25)	1-10, 17-21, 24,25, 27,28,36
A	page 14, line 16, paragraph 9 -page 17, line 24, paragraph 16 page 31, line 30 -page 34, line 12 page 41, line 1 -page 46, line 1 page 63, line 7 -page 64, line 43	29
A	FUJIBUCHI W ET AL: "KEGG AND DBGET/LINKBD: INTEGRATION OF BIOLOGICAL RELATIONSHIPS IN DIVERGENT MOLECULAR BIOLOGY DATA" KNOWLEDGE SHARING ACROSS BIOLOGICAL AND MEDICAL KNOWLEDGE BASED SYSTEMS. TECHNICAL REPORT,XX,XX, 1998, pages 35-40, XP000890026 page 36, left-hand column, line 2 -page 40, left-hand column, line 9	17,21, 22,29-35
A	KARP P D: "Database links are a foundation for interoperability" TRENDS IN BIOTECHNOLOGY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 14, no. 8, 1 August 1996 (1996-08-01), pages 273-279, XP004035744 ISSN: 0167-7799 page 274, right-hand column, line 1 -page 277, right-hand column, line 6; tables BOX-1	1-36
A	PALEY S M ET AL: "Adapting EcoCyc for use on the World Wide Web" GENE,NL,ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, vol. 172, no. 1, 12 June 1996 (1996-06-12), pages GC43-GC50, XP004042696 ISSN: 0378-1119 abstract page 43, left-hand column, line 1 -page 46, left-hand column, line 3; figure 2	1-36
A	KARP P D: "Metabolic databases" TIBS TRENDS IN BIOCHEMICAL SCIENCES,EN,ELSEVIER PUBLICATION, CAMBRIDGE, vol. 23, no. 3, 1 March 1998 (1998-03-01), pages 114-116, XP004111317 ISSN: 0968-0004 the whole document	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/04331

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9622575 A	25-07-1996	US 5980096 A	09-11-1999
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